Prolongation of regional anesthesia

Determinants of peripheral nerve block duration

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Chapter 01

Introduction and outline of the thesis

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Introduction and outline of the thesis

In the past years, peripheral nerve block has rapidly gained popularity as an anesthetic technique for i.a. upper and lower extremity orthopedic surgery. It is popular among anesthesiologists and patients for peri- and postoperative pain relief. By blocking specific nerves to the limb that is to be operated, locoregional anesthesia and analgesia can be achieved. The choice of anesthetic technique is determined by patient comorbidities and by obtaining an informed consent that includes understanding all available options and their risks and benefits. Compared to general anesthesia or central neuraxis blockade, interference of peripheral nerve block with vital functions is minimal and postoperative analgesia is excellent. If a patient has significant comorbidity, peripheral nerve block may have advantages over general anesthesia, e.g. the use of axillary block for hand surgery in a respiratory cripple.

Regional anesthetic techniques play an important role in providing postoperative analgesia, decreasing the incidence of perioperative thromboembolic complications and facilitating early rehabilitation and hospital discharges. The use of peripheral nerve blocks is increasing; they are being used as the primary and sole anesthetic technique to facilitate painless surgery whether or not supplemented with sedation or a 'light' general anesthetic, with the airway protected with a laryngeal mask airway. Regional anesthesia may also be instituted preoperatively with the sole objective of postoperative analgesia.

"Regional anesthesia always works, provided you put the right dose of the right drug in the right place."[1] This chapter provides some background information about the relevant anatomy and the techniques and local anesthetics used for regional anesthesia. This thesis discusses different factors determining the duration of peripheral nerve block.

Anatomy

Surgical anesthesia of the upper extremity and shoulder can be obtained by neural blockade of the brachial plexus (C5-Th1) or its terminal branches at several sites. The brachial plexus (Figure 1) is formed by the union of the anterior primary divisions (ventral rami) of the fifth through the eighth cervical roots and the first thoracic root (A). As the nerve roots leave the intervertebral foramina, they converge, forming trunks, divisions, cords, and then finally terminal nerves. Three distinct trunks are formed between the anterior and middle scalene muscles. Because they are vertically arranged, they are termed superior, middle and inferior (B). As the trunks pass over the lateral border of the first rib and under the clavicle, each trunk divides into anterior and posterior divisions (C). As the brachial plexus emerges below the clavicle, the fibers combine again to form three cords that are named according to their relationship to the subclavian artery: lateral, medial, and posterior (D). At the lateral border of the pectoralis minor muscle, each cord gives off a large branch before terminating as a major terminal nerve (E). The lateral cord gives off the lateral branch of the median nerve and terminates as the musculocutaneous nerve; the medial cord gives off the medial branch of the median nerve and terminates as the ulnar nerve; and the posterior cord gives off the axillary nerve and terminates as the radial nerve.

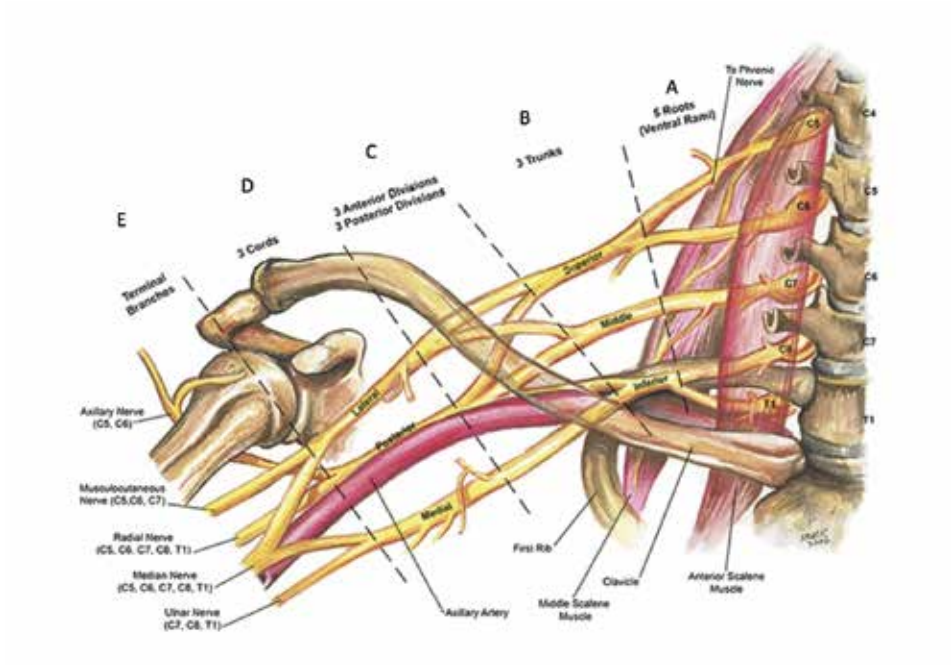

Figure 1. Brachial plexus anatomy.
Original illustration was created by Lieutenant Michael K. Sracic, MD, MC, US Navy for *Military Advanced Regional Anesthesia and Analgesia Handbook@* 2008 The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and is reproduced with permission.

The lumbar and sacral plexuses are the major nerve distributions to the lower extremities. The lumbar plexus is derived from the ventral rami of L1-L4, with some occasional contribution from T12 (Figure 2, 3). The lumbar plexus, forms three major nerves that innervate the lower extremity: the lateral femoral cutaneous, femoral and obturator nerves. These nerves predominantly supply motor and sensory innervation to the anterior portion of the lower extremity and the cutaneous sensory portion of the medial lower leg (saphenous nerve). The femoral nerve runs between the psoas and iliacus muscles to enter the thigh beneath the inguinal ligament, 1-2 cm lateral to the femoral artery and at a slightly greater depth.

The sacral plexus is derived from the nerve roots of L4-L5 and S1-S3 (Figure 2, 3). It primarily forms the sciatic nerve, which passes through the greater sciatic foramen and descends in the posterior thigh to the popliteal fossa, where it divides into the tibial and common peroneal nerve and supplies both motor and sensory innervation to the posterior aspect of the lower extremity and foot.

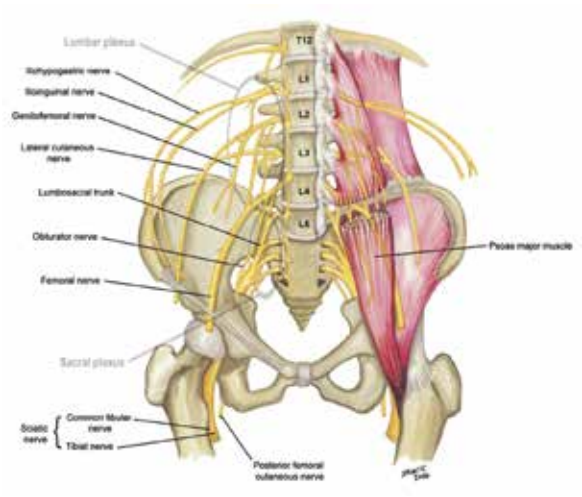

Figure 2.
Lumbosacral plexus anatomy
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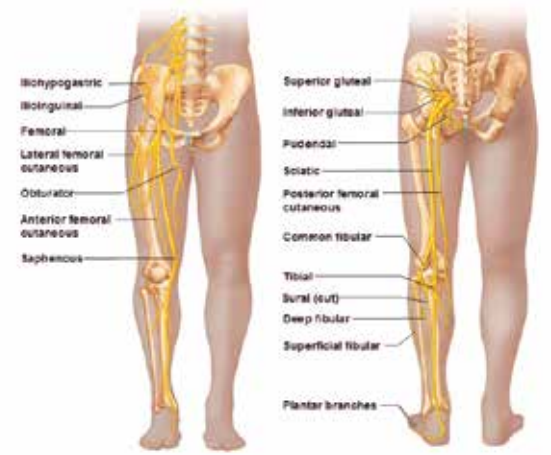

Figure 3.
Innervation of the lower extremity
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Technique

Fundamental to the success of peripheral nerve block is the correct positioning of the needle tip in proximity to the nerve, prior to injection of local anesthetic. This is accomplished by the use of ultrasound localization and/or nerve electrostimulation. Before the introduction of ultrasound, a nerve stimulator was used to identify proximity to the nerves and before that, needles were inserted using landmarks, inducing paresthesia or a facial 'click'.

Low-level electrical current applied from the tip of a needle can elicit specific muscle contractions when the needle is in close proximity to a motor nerve. One lead of a low-output nerve stimulator is attached to a needle and the other lead is grounded elsewhere on the patient's skin. After skin puncture, the stimulator is set to a frequency of 1 Hz and an initial current of 100 nC (1 mA x 0.1 ms). A pulse width of 0.1 ms is chosen because it is sufficient for stimulation of motor fibers without stimulating sensory fibers, which may be uncomfortable for the patient. Muscle contractions occur and increase in intensity as the needle approaches the nerve and diminish when the needle moves away. Optimal positioning produces evoked

contractions between 20 and 50 nC. Characteristically, the evoked response rapidly fades after injection of a few milliliters of local anesthetic. However, the sensitivity of nerve stimulation as a means of identifying proximity of the needle tip to the nerve is not 100%. Perlas et al.[2] found that only 75% had a motor response at a current threshold less than 50 nC, despite visible needle-nerve contact during ultrasounds-guided axillary block. Nonetheless, electrostimulation is still considered a useful tool in conjunction with ultrasound, especially for confirming nerve identity.[3]

The introduction of ultrasound has changed the practice of peripheral nerve block. Ultrasound offers the ability to visualize relevant anatomical structures, needle advancement, needle – nerve interaction, and local anesthetic spread in real time.[4] Using ultrasound guidance, local anesthetic spread around the nerves can be visualized with the possibility of repositioning the needle in case of maldistribution,[5] allowing for a reduction in local anesthetic dose without compromising the quality of the peripheral nerve block. Recent publications indeed illustrate that the volume of local anesthetic can be significantly reduced when particular regional anesthetic techniques are performed with ultrasound guidance.[6-9] This may in turn reduce the risk of local anesthetic systemic toxicity, and of unintentional blockade of other nerves in the vicinity.[3]

Sometimes extended duration of peripheral nerve block is desirable, f.e. when prolonged postoperative pain is expected, or to prevent the need for postoperative systemic analgesia. In that case, peripheral nerve block can be administered continuously using a catheter. A meta-analysis comparing continuous peripheral nerve block versus single shot peripheral nerve block shows that continuous peripheral nerve block offers superior pain control, less nausea, and higher patient satisfaction, with decreased opioid consumption during the initial postoperative period.[10]
Continuous peripheral nerve blocks provide superior pain relief for several days after painful surgical procedures; they facilitate early rehabilitation[11,12] and may decrease adverse effects related to systemic analgesic medications.[13,14]

For continuous peripheral nerve block, non-stimulating and stimulating catheters are available. Non-stimulating catheters are inserted blindly through the needle after obtaining a correct needle position as determined by nerve stimulation and/or ultrasound visualization. Stimulating catheters can be inserted while stimulating at the tip of the catheter. The expected added value of stimulation during insertion is that by maintaining an appropriate motor response, optimal positioning of the tip in close proximity of the nerve can be ensured.[15]

Local anesthetics

When performing a peripheral nerve block, the anesthesiologist must decide on the specific local anesthetic agent(s) as well as the volume, concentration and dose to be injected. The choice of local anesthetic in peripheral nerve block is mainly determined by the desired speed of onset, block intensity (potency), duration of anesthesia and analgesia and toxicity.[16]

Chemical structure

All local anesthetic molecules in clinical use have three parts: a lipophilic (aromatic) ring, a hydrophilic terminal amine, and an intermediate linkage between the aromatic ring and the terminal amine. The link contains either an aminoester or an aminoamide bond, and local anesthetics are designated as belonging to one of two groups: aminoesters or aminoamides. All drugs known and used as local anesthetics have originated form cocaine, the alkaloid found in the leaves of the South American bush *Erythroxylon coca*. Its local anesthetic action was first demonstrated in 1884 by Koller, a resident with an interest in ophthalmology in the General Hospital in Vienna.[17] That same year, the American surgeons Halsted and Hall performed the first sensory nerve blocks by injecting cocaine into peripheral sites.[18] The drug lost its popularity because of its systemic toxicity, central nervous stimulant and addictive properties and tendency to produce allergic reactions. Fundamental to the development of safer synthetic local anesthetics was the demonstration of the physical structure of cocaine as an ester of benzoic acid.[19] Procaine, one of the first synthetic local anesthetics, was synthesized by the German chemist Einhorn in 1905.[20] Concerning the local anesthetics used in this thesis, mepivacaine was first mentioned in the literature in 1956[21] and the first trials with ropivacaine followed much later in 1983.[22]

Mechanism of action

Local anesthetics act by reversibly blocking voltage-gated sodium channels in axons in all excitable tissues. When stimulated, a depolarization in an axon membrane opens the voltage gated sodium channels. Blockade of these channels prevents sodium (Na+) movement through the sodium channel and interrupts membrane depolarization and thus blocks nerve conduction.[23]

Absorption, distribution and metabolism

The changes in plasma concentration of drug following injection are dependent on the total dose administered, the rate of absorption, the pattern of distribution to other tissues, and the rate of metabolism. Vascularity and the presence of tissue and fat capable of binding local anesthetics will be the main determinants of the rate of removal of the drug from the site of injection.[23] Absorption from the site of injection depends on the blood flow; the higher the blood flow, the more rapid is the increase in plasma concentration. Blood flow may be modified by vasoactive properties of the drug itself or by the addition of vasocontrictors such as epinephrine to the solution.[24]

After absorption, local anesthetics are distributed rapidly to, and taken up by, organs with a large blood supply and high affinity, e.g. brain, heart, liver and lungs. Local anesthetic drugs are sequestered in (and possibly metabolized in) the lungs, thereby preventing a large proportion of the injected dose from reaching the coronary and cerebral circulations. Eventually, tissue concentration of local anesthetic decreases below that in the nerve fibers and the drug diffuses out, so allowing restoration of normal nerve function.[25]

Ester drugs are broken down by plasma cholinesterase (hydrolyzed by esterases in tissues and blood). The amides are metabolized by amidases (microsomal P-450 enzymes) located predominantly in the liver.[25]

Differences in the clinical profiles of individual agents (onset, potency, duration of action, etc) are related to variations in the physiochemical properties. The important factors are the pK_a (onset), lipid solubility (potency and duration of action) and degree of binding to protein (toxicity).

Clinical profiles

Speed of onset – pK_a

Local anesthetics are weak bases. There is a balance between uncharged (free base, LA) and positively charged (cation, LAH+) forms present in the body. The ratio of cation to free base is determined by the pK_a of the local anesthetic and the pH of the solution. The pK_a is the pH at which 50% of the drug is ionized and 50% is present as base.[25] Increasing the pH of a solution increases the ratio of free base to cation. Commercial solutions of local anesthetics are usually injected in an acid solution as the hydrochloride salt (pH approximately 5), so the hydrophilic (cationic, LAH+) state is favored. After injection, the pH increases as a result of buffering in the tissues and a proportion of the drug dissociates to release free base.[25] The uncharged free base is more lipophilic and thus more rapidly diffuses through the membrane to the interior of the axon, where re-ionization takes place. The charged form has a higher affinity for the receptor site of the sodium channel and it is this re-ionized portion that enters and blocks the sodium channels (Figure 4). As a result, no action potential is generated or transmitted, and conduction blockade occurs. A low pK_a favors rapid onset of action because more of the drug is uncharged at physiological pH and is thus lipid permeant.[25]

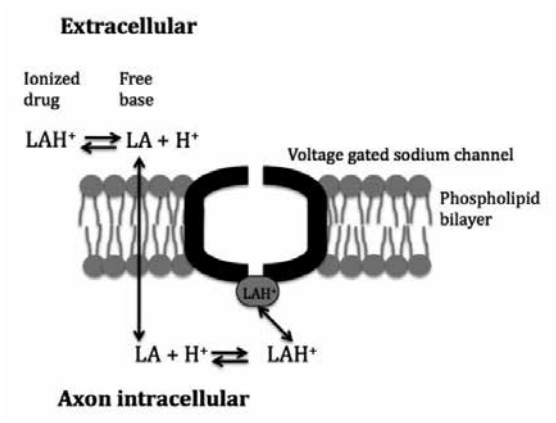

Figure 4. Local anesthetic interaction with sodium channel

Potency and duration of action – Lipid solubility and vasoconstriction

Duration of action is related to the extent to which local anesthetic remains in the vicinity of the nerve. This is determined largely by three factors; lipid solubility the degree of vascularity of the tissue and the presence of vasocontrictors that prevent vascular uptake. The more lipid soluble the drug, the more likely it will remain in the lipid-rich environment of the axonal membrane. There is a positive correlation between lipid solubility of local anesthetics and intrinsic local anesthetic potency.[23] Chemical compounds which are highly lipophilic tend to penetrate the nerve membrane more easily, so that less molecules are required for conduction blockade. They are more potent and produce longer acting blockade than less lipophilic agents.[26]

More lipophilic agents are attracted to plasma proteins to a greater extent than less lipophilic agents.
Therefore, there is a direct correlation between protein binding and lipid solubility. This means that duration of action relates to the degree of protein binding with a longer duration of action in drugs with a higher fraction of protein binding.[23]

Block duration is further determined by the degree of vascularity of the tissue and the presence of vasoconstrictors that prevent vascular uptake. This varies significantly among individual nerve blocks and different types of local anesthetics. The addition of a vasoconstrictor to a local anesthetic delays its vascular absorption, increasing the duration of drug being in vicinity of nerve tissues. Also, intrinsic vasoactive properties relate to duration of action. The vasoconstriction at low concentrations of ropivacaine is likely to contribute to its long duration of action.[27]

Toxicity - Protein binding

Local anesthetics are in large part bound to plasma and tissue proteins. However, they are pharmacologically active only in the free unbound state. The main plasma proteins involved in drug binding are albumin, α_1-acid glycoprotein (AAG) and the lipoproteins, with AAG being primarily responsible for the binding of basic drugs, such as local anesthetics.[23] Plasma concentrations of AAG are increased as a result of various pathophysiological conditions, such as surgery, trauma and certain disease states, with a subsequent rise in plasma protein binding.[28]

Local anesthetics are bound to plasma proteins to varying degrees. Drugs with the greatest degrees of protein binding have the smallest fraction of the total amount in plasma free to diffuse into other tissues and possibly produce toxic effects. Toxicity of local anesthetics is mostly related to their inhibitory effects on other excitable cells in the central nervous and cardiovascular system.[24] Following absorption, local anesthetics cause stimulation of the central nervous system, such as auditory changes, circumoral numbness, metallic taste, and agitation. Stimulation is caused by inhibition of inhibitor neuronal activity of the higher cortical centers. At high blood concentrations, local anesthetics cause central nervous system depression and even respiratory failure. In the cardiovascular system, local anesthetics cause cardiac excitation (hypertension, tachycardia, ventricular arrhythmias). With greatly increased blood concentrations, cardiac excitation may be followed by cardiac depression (bradycardia, asystole, decreased contractility, and hypotension).[29]

Duration of peripheral nerve blocks: Focus and outline of the thesis

Duration of peripheral nerve block depends on several factors such as the choice of local anesthetic, the presence of adjuncts such as epinephrine or clonidine, and the use of a catheter for prolonged infusion. Choices can be made dependent on the purpose of the nerve block; is it for intraoperative anesthesia and/or should it provide (prolonged) postoperative analgesia.

Intraoperative anesthesia for minimally painful surgery: short acting local anesthetics

If the goal is to provide surgical anesthesia for minimally painful surgery, a short acting local anesthetic can be used. From a safety perspective a lower dose is preferable and using ultrasound guidance, adequate peripheral nerve block can be established with a lower volume. In **Chapter 2** we evaluated the effect of the volume of mepivacaine 1.5% on the duration of sensory and motor block in ultrasound-guided axillary brachial plexus block. We designed the study in **Chapter 3** to determine if a similar dose administered in different volumes and concentrations would affect the duration of sensory and motor block in axillary brachial plexus block, as well as if different doses administered in a similar volume would have any effect.

Intraoperative anesthesia and postoperative analgesia: long acting local anesthetics with additives

For surgery where some postoperative pain is expected, a longer acting local anesthetic can be used. This can provide surgical anesthesia and cover the first postoperative hours in terms of postoperative analgesia. To optimize safety, epinephrine can be added to large doses of ropivacaine in order to reduce the maximum concentration or to act as a marker for intravascular injection. In **Chapter 4** we describe the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine, in patients undergoing anterior cruciate ligament reconstruction under single-shot combined sciatic/femoral nerve block. The purpose of **Chapter 5** is to compare the duration of postoperative analgesia of 30 mL ropivacaine 0.75% with or without epinephrine for popliteal sciatic nerve block. In this study a nerve catheter is inserted to provide prolonged postoperative analgesia.

Postoperative prolonged action with a perineural catheter

If postoperative pain is expected to be severe and longer lasting, e.g. in arthroplasty, a nerve catheter can be inserted for prolonged infusion of local anesthetic. For continuous nerve block, stimulating and non-stimulating catheters can be used. In **Chapter 6** we investigated whether there is a correlation between the minimal electrical charge at the tip of a blindly inserted stimulating catheter necessary to elicit an appropriate motor response, and the efficacy of the peripheral nerve block catheter as determined by postoperative PCA morphine consumption.

Chapter 7 of this thesis summarizes and discusses our main findings in relation to the current literature and gives recommendations for future research.

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Chapter 02

Effect of local anesthetic volume (15 vs 40 mL) on the duration of ultrasound-guided single shot axillary brachial plexus block: a prospective randomized observer-blinded trial

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Abstract

Background: One of the advantages of ultrasound-guided peripheral nerve block is that visualization of local anesthetic spread allows for a reduction in dose. However, little is known about the effect of dose reduction on sensory and motor block duration. The purpose of the present study was to compare the duration of sensory and motor axillary brachial plexus block with 15 or 40 mL mepivacaine 1.5%.

Methods: Thirty patients were randomly allocated to receive ultrasound-guided axillary brachial plexus block with either 15 (group 15 mL, n = 15) or 40 mL (group 40 mL, n = 15) mepivacaine 1.5%. Onset, efficacy and duration of sensory and motor block were compared.

Results: Two patients in group 15 mL needed an additional rescue block before surgery and were excluded from subsequent analysis. The median overall duration of sensory and motor block was significantly shorter in group 15 mL (225 [148-265] mins vs 271[210-401] mins and 217 [144-250] mins vs 269 [210-401] mins respectively, $P < 0.01$). Duration of sensory and motor block of individual nerves was significantly shorter in group 15 mL (20%-40% reduction for sensory and 18%-37% for motor block). Time to first request of postoperative analgesia was also significantly reduced in group 15 mL (163 [SD, 39] versus 235 [SD, 59] mins, respectively, $P < 0.05$). There were no differences in the other block characteristics.

Conclusions: In ABPB with mepivacaine 1.5%, reducing the dose from 40 mL to 15 mL (62.5%) shortens the overall duration of sensory and motor block by approximately 17%-19%, reduces sensory and motor block duration of individual nerves by 18% to 40%, and decreases the time to first request of postoperative analgesia by approximately 30%.

Introduction

Peripheral nerve block as an anesthetic technique plays an important role in modern regional anesthesia. The most important prerequisites for the use of peripheral regional anesthesia in daily clinical practice are success rate and safety. Ultrasound guidance shortens block performance time, reduces the number of needle insertions, and shortens the block onset time.[1] Recent publications illustrate that the volume of local anesthetic can be significantly reduced with the use of ultrasound.[2-10]

Axillary brachial plexus block (ABPB) is widely used to provide anesthesia for surgery of the forearm, wrist, and hand. The procedure is relatively safe and complications are uncommon.[11] Before the introduction of ultrasound, volumes of 40 mL or even more were commonly used.[12] Recent research has focused on reducing the volume necessary to establish adequate ABPB. Volumes of 5 mL per nerve[13] or even as low as 1 mL lidocaine 2% per nerve[8] have been reported to achieve successful ABPB. However, the effect of dose reduction on block duration remains unknown.

The purpose of the present study was to evaluate the effect of the volume of mepivacaine 1.5% on the duration of sensory and motor block in ultrasound-guided ABPB.

Materials and Methods

Patients

This prospective single-blinded, randomized study was approved by the Institutional Review Board Nijmegen and registered at http://www.trialregister.nl (NTR2371) before participant enrollment. Patients scheduled for a single shot ABPB for hand, wrist, or forearm surgery were assessed for eligibility during the preoperative screening visit. Patients were informed about the study verbally and in writing, and written informed consent was obtained from all patients. The study was conducted at the Sint Maartenskliniek, Nijmegen, the Netherlands, between July 2010 and March 2011 in accordance with the Declaration of Helsinki and later revisions thereof, as well as ICH guidelines for Good Clinical Practice.

Eligible participants were adults 18 years or older with American Society of Anesthesiologists physical health classification I-III and a body weight greater than 50 kg. Exclusion criteria included contraindications for regional anesthesia (infection at the injection site, coagulopathy), known hypersensitivity to amide-type local anesthetics, known history of peripheral neuropathy, and known history of hepatic or renal insufficiency.

Anesthetic procedure

All patients received paracetamol 1000 mg orally 3 times daily and meloxicam 15 mg orally once daily, starting on the morning of surgery. Additional postoperative pain treatment was provided upon patient request and consisted of oxycodone 10 mg orally 4 to 6 times daily.

Using a computer-generated sequence of random numbers and a sealed envelope technique, 30 patients were randomly allocated to receive ultrasound-guided ABPB with either 15 (group 15 mL, n = 15) or 40 mL (group 40 mL, n = 15) mepivacaine 1.5%. After establishing intravenous access and routine monitoring (electrocardiogram, noninvasive blood pressure, and peripheral oxygen saturation), ABPB was performed under ultrasound guidance (L12-5 linear probe connected to Philips HD11 XE; Philips, Eindhoven, the Netherlands) using a short axis, in-plane technique. Blocks were performed under aseptic conditions using chlorhexidine skin preparation and sterile ultrasound probe covers (Flexasoft; Medicocare, Numansdorp, the Netherlands).

A 100-mm, 22-gauge, insulated short-bevel needle (Stimuplex B. Braun, Melsungen, Germany) was inserted laterally in the axilla. The needle was connected to a nerve stimulator (Stimuplex HNS 11; B. Braun) that was set to deliver 100 nC (0.1 millisecond, 1 mA), only to facilitate identification of the individual nerves. After identifying the musculocutaneous, median, ulnar, and radial nerves, each nerve was blocked with either 10 mL (40 mL group) or 3 to 4 mL (15 mL group) mepivacaine 1.5%.
Time was designated t = 0 upon conclusion of the block procedure.

Clinical assessments

In the first 30 mins after injection of the local anesthetic solution, a blinded observer assessed the onset of sensory and motor block every 5 mins. Sensory block of the medial antebrachial cutaneous, musculocutaneous, radial, median, and ulnar nerves was assessed by pinprick at specific sites (Table 1). Sensory block was scored on a 3-point scale as 0 = absent, 1 = partial, and 2 = complete. At the same intervals, motor block of the musculocutaneous, radial, median, and ulnar nerves was assessed (Table 1) on a similar 3-point scale (0 = no, 1 = partial, and 2 = complete motor block). A complete overall sensory block was defined as a total score of 10; complete overall motor block was defined as a total score of 8. In case of insufficient analgesia at the surgical site at t = 30 mins, an additional rescue block was placed in the block room, and the patient was excluded from further analysis.

Table 1. Sensory and Motor Testing

Nerve	Sensory test site	Motor test
Medial antebrachial cutaneous	Medial side forearm	-
Musculocutaneous	Lateral side forearm	Elbow flexion
Radial	Dorsum of hand	Wrist extension
Median	Ventral top of middle finger	Thumb opposition
Ulnar	Hypothenar eminence	Finger abduction

Surgery was performed under regional anesthesia. In the case of patient discomfort or upon patient request, sedation was provided with propofol (25-60 μg/kg per minute) and remifentanil (0.01-0.05 μg/kg per minute). If sedation was insufficient in case for patient discomfort, patients were converted to general anesthesia.
Upon arrival at the recovery room, offset of sensory and motor block was assessed by a blinded observer every 15 mins in the same manner as preoperatively until full recovery.
The primary outcome parameter was overall duration of sensory block. Overall duration of sensory block was defined as the time from *t* = 0 until the first postoperative measurement where total sensory score had returned to 0. Overall duration of motor block was defined similarly. Duration of sensory and motor block of individual nerves was defined as the time from *t* = 0 until the first postoperative measurement where the sensory and motor score for the individual nerve was 0. Secondary outcome parameters included overall duration of motor block, duration of sensory and motor block of individual nerves, block onset time, block efficacy and time to first request for additional postoperative pain treatment (TTFR).

Block onset time was defined as the time from *t* = 0 until the time sensory, respectively, motor score was maximal. Block efficacy during surgery was assessed as successful (no intraoperative sedation necessary), partially successful (intraoperative sedation necessary), or unsuccessful (conversion to general anesthesia). Time to first request for additional postoperative pain treatment was defined as the time interval from *t* = 0 until the time the first request for postoperative analgesia was made.

Sample size and statistical analysis

The sample size calculation was based on the overall duration of sensory block. Robaux et al.[14] found a sensory duration of ABPB (with 40 mL mepivacaine 1.5%) of 183 (SD, 43) mins. Based on these data, the sample size required to have a 90% probability of detecting a decrease in duration of 60 min (level of significance 0.05) was 12 patients per group using an unpaired t test. Compensating for dropout, we chose to include 15 patients per group.
Analysis was per protocol. Data were analyzed using the GraphPad InStat v. 3.10 package (GraphPad Software Inc, San Diego, California). The Kolmogorov-Smirnov test was used for normality testing. Continuous, normally distributed data were presented as mean (SD), and non-normally distributed data as median (range). Statistical comparison between the groups was based on the Student *t* test for normally distributed data, and the Mann-Whitney *U* test for nonparametric comparisons. For comparisons within groups, normally distributed data were compared using the 1-way analysis of variance, and non-normally distributed data using the Kruskal-Wallis test. Post hoc comparisons were made using Tukey-Kramer or Dunn multiple comparisons test as appropriate. Categorical data were compared using Fisher exact test. In case where a parameter was normally distributed in 1 group and nonnormally in the other group, the data are presented as median (range) and a nonparametric test was used for statistical comparison. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

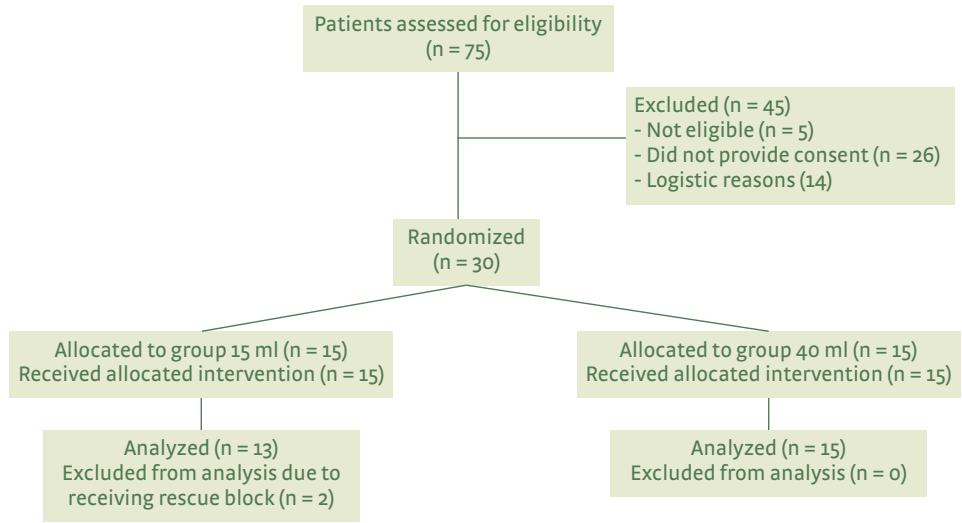

Figure 1. Flowchart of patients enrolled in the study.

Results

Thirty patients were included, 15 in each group. A flowchart of patients enrolled in this study is presented in Figure 1. In group 15 mL, 2 patients needed a rescue block before surgery because of incomplete block in the surgical area, compared with 0 patients in group 40 mL. These 2 patients were excluded from subsequent analysis. There were no significant differences in patient demographics between the 2 groups (Table 2).

Table 2. Baseline Characteristics

	Group 15 mL (n=13)	Group 40 mL (n=15)
Sex, no. male/no. female	5/8	4/11
Age, y	53 (16)	55 (9)
Height, cm	171 (9)	173 (8)
Weight, kg	76 (13)	78 (14)
Body mass index, kg/m^2	25.8 (3.7)	25.8 (2.8)
Duration of surgery, min	23.2 (15.6)	21.5 (10.7)

Group 15 mL: axillary brachial plexus block with 15 mL mepivacaine 1.5%. Group 40 mL: axillary brachial plexus block with 40 mL mepivacaine 1.5%. Values are numbers or mean (SD).

On 7 time points postoperatively, we were unable to obtain a measurement of sensory and motor blocks in 6 patients because of temporary patient unavailability. In 5 patients, these missing data did not affect the outcome parameters because sensory and motor blocks were still present at the next measurement. In 1 patient (group 40 mL), we missed 2 consecutive measurements during which both sensory and motor blocks had completely resolved. In this patient, we took the first time point following the missing data to calculate overall block duration; replacing this time point with the first time point where we were unable to obtain a measurement (30 mins earlier) revealed that this did not significantly affect the results.

Block characteristics

Thirty minutes after block placement 7 of 13 patients in group 15 mL had a complete sensory block (maximum score of 10) versus 9 of 15 patients in group 40 mL (not statistically significant [NS]). Onset of complete sensory block was 21 (SD, 5) mins in group 15 mL (n = 7) and 22 (SD, 6) mins in group 40 mL (n = 9) (NS). After 30 mins, motor block was complete (maximum score of 8) in 8 of 13 patients in group 15 mL versus 11 of 15 patients in group 40 mL (NS). Onset of complete motor block was 22 (SD, 8) mins and 23 (SD, 7) mins in group 15 mL (n = 8) and group 40 mL (n = 11), respectively (NS). There were no significant differences between the groups in the onset times of sensory/motor block of individual nerves. Data on sensory and motor block scores of individual nerves are shown in Table 3.

Table 3. Block Scores of Individual Nerves at 30 mins

Nerve	Group 15 mL (n = 13)			Group 40 mL (n = 15)		
	Score 2	Score 1	Score 0	Score 2	Score 1	Score 0
Med. anteb. cut. sens	11	2	-	14	1	-
Musculocutaneous sens	12	1	-	12	3	-
Musculocutaneous mot	9	4	-	13	2	-
Radial sens	10	3	-	12	3	-
Radial mot	11	2	-	11	4	-
Median sens	11	2	-	14	1	-
Median mot	11	2	-	15	-	-
Ulnar sens	11	2	-	15	-	-
Ulnar mot	11	2	-	14	1	-

Groups as defined in Table 2. Values are numbers. Med. anteb. cut. indicates medial antebrachial cutaneous nerve; sens, sensory block score; mot, motor block score.

The median overall duration of sensory block in group 40 mL was 271 (range, 210-401) mins versus 225 (range, 148-265) min in group 15 mL ($P < 0.001$). The median overall duration of motor block was 269 (range, 210-401) mins in group 40 mL versus 217 (range, 144-250) mins in group 15 mL ($P < 0.001$). Overall duration was largely determined by the duration of sensory and motor block of the ulnar nerve. In 10 of 13 patients in group 15 mL and 10 of 15 patients in group 40 mL, the ulnar nerve was among the last to recover. Within each group, there were no significant differences in the duration of sensory and motor block between the individual nerves. Between groups, the duration of both sensory and motor blocks for each individual nerve was significantly longer in group 40 mL. Data on overall and individual block characteristics are summarized in Table 4 and Figures 2-4.

Twelve patients, 6 in each group, requested additional postoperative analgesia. Time to first request for additional postoperative pain treatment was significantly shorter in group 15 mL (163 [SD, 39] mins) as compared to group 40 mL (235 [SD, 59] mins) ($P < 0.05$). Twenty-five patients underwent surgery without need for additional sedation. Three patients, 2 in group 15 mL and 1 patient in group 40 mL, needed sedation because of patient discomfort. None of the patients required conversion to general anesthesia.

Table 4. Sensory and Motor Block Duration of Individual Nerves

	Group 15 mL (n = 13)	Group 40 mL (n = 15)	*P*	Difference,* %
Overall sensory block duration	225 (148-265)	271 (210-401)	<0.001	17
Overall motor block duration	217 (144-250)	269 (210-401)	<0.001	19
Med. anteb. cut. nerve				
Sensory block, min	157 (98-235)	262 (191-301)	< 0.0001	40
Musculocutaneous nerve				
Sensory block, min	154 (68-235)	247 (151-296)	< 0.01	38
Motor block, min	160 (114-233)	254 (150-311)	< 0.0001	37
Radial nerve				
Sensory block, min	173 (103-235)	235 (177-401)	< 0.001	26
Motor block, min	190 (114-225)	262 (150-351)	< 0.001	27
Median nerve				
Sensory block, min	184 (133-265)	241 (192-349)	< 0.001	24
Motor block, min	173 (129-235)	245 (207-301)	< 0.001	29
Ulnar nerve				
Sensory block, min	202 (148-250)	252 (210-351)	< 0.001	20
Motor block, min	210 (144-250)	256 (210-401)	< 0.001	18

Groups as defined in Table 2. Values are median (range). *Difference, difference between the medians of group 40 mL and group 15 mL as a percentage of the median value of group 40 mL. Med. anteb. aut. nerve indicates medial antebrachial cutaneous nerve.

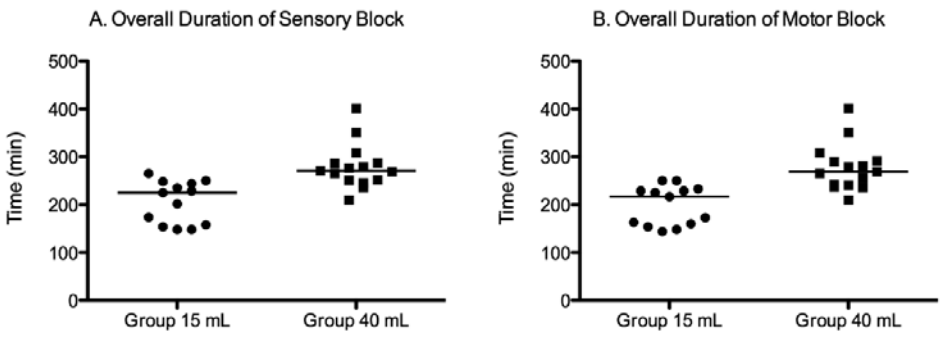

Figure 2. Duration of overall sensory (A) and motor (B) block.
Dots are individual data, horizontal bars represent median values.

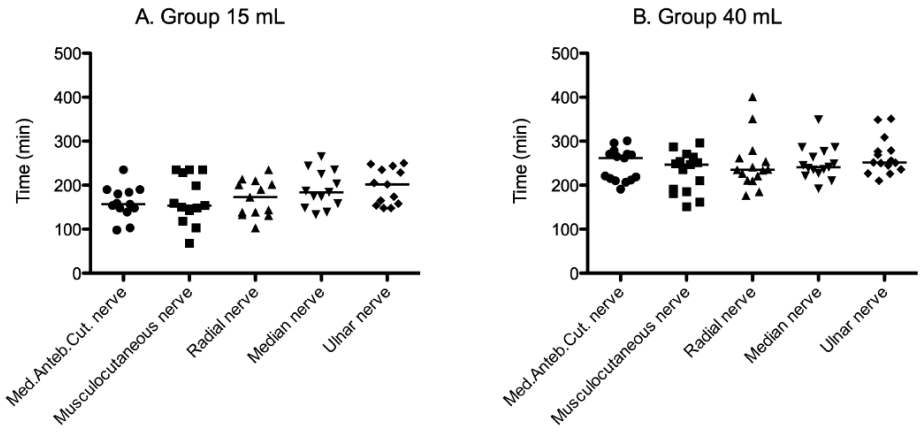

Figure 3. Duration of sensory block of individual nerves in group 15 mL (A) and group 40 mL (B).
Dots are individual data; horizontal bars represent median values. Med. anteb. cut. indicates medial antebrachial cutaneous nerve.

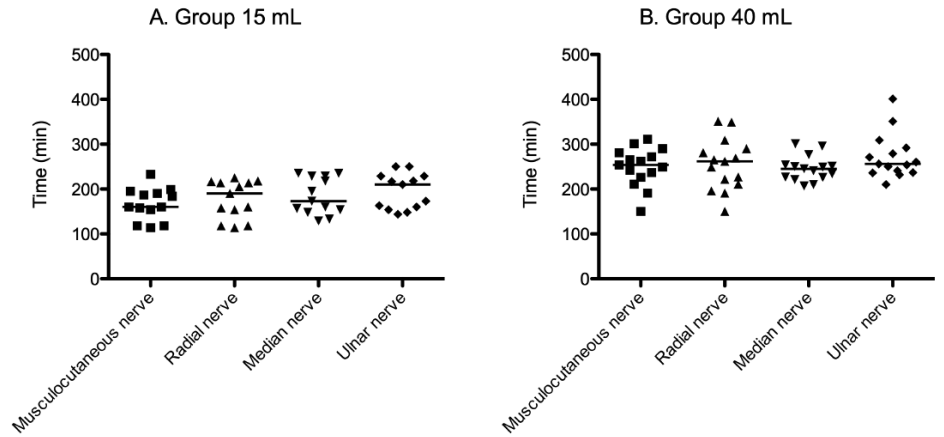

Figure 4. Duration of motor block of individual nerves in group 15 mL (A) and group 40 mL (B).
Dots are individual data; horizontal bars represent median values.

Discussion

In the present investigation, a local anesthetic volume reduction of 60% resulted in an approximately 17% shorter overall sensory and 19% motor block duration and a reduction in TTFR of approximately 30%. Because overall duration is determined by the last nerve to recover, this parameter may underestimate the effect of a reduction in dose. Indeed, we found that the reduction in duration for individual nerves was larger, varying from 20% to 40% for sensory block and from 18% to 37% for motor block. The ulnar nerve was least affected by the reduction in dose; the 2 nerves most strongly affected were the medial antebrachial cutaneous and musculocutaneous nerves.

Duration of peripheral nerve block depends on several factors, such as the choice of local anesthetic, the site of injection and the presence of adjuncts, for example clonidine or epinephrine. Some studies in children implicate that the use of ultrasound guidance itself provides a longer duration of sensory blockade compared with nerve stimulation without ultrasound.[15,16] The dose of local anesthetic administered when performing peripheral nerve block is determined by volume and concentration; the manner in which these parameters affect duration is controversial. In a study aimed to determine the minimum effective anesthetic volume for blocking the median and ulnar nerve with mepivacaine 1.5%, Ponrouch et al[17] found that the use of ultrasound as compared with nerve stimulation reduced the effective anesthetic volume by 50%. They also found a significant correlation between the volume of local anesthetic and the duration of sensory blockade, the correlation being higher with lower volumes. Similar findings were reported in a volunteer study designed to determine the ED99 volume of mepivacaine 1.5% for sciatic nerve block, showing a proportional relation between volume of local anesthetic per millimeter squared cross-sectional nerve area and duration of sensory block.[18] In a study comparing low-volume (16 mL) ultrasound-guided ankle block with a conventional higher-volume (30 mL) landmark technique using ropivacaine 0.5%, Fredrickson et al[19] found that average postoperative pain was marginally higher in the low-volume group. Although the authors did not measure block duration or the time to first request of postoperative analgesia directly, the results suggest a shorter duration of sensory block associated with the low-volume group.

On the other hand, Serradell et al[20] compared the number of complete sensory blocks for different volumes (20, 28, 36 mL) of mepivacaine 1% in axillary block and found no differences in success rate, onset time, and duration of analgesia among the 3 groups. The results of the latter study suggest that 200 mg mepivacaine in a volume of 20 mL provides adequate axillary block and that increasing the volume/dose of mepivacaine to 280 or 360 mg does not result in a higher success rate or a longer duration of analgesia. Duration of analgesia reported by Serradell et al[20] was 231 (SD, 45) mins in their group receiving axillary block with 200 mg mepivacaine in 20 mL. Interestingly, the TTFR in our group 40 mL (600 mg mepivacaine) was similar (235 [SD, 59] mins), whereas the TTFR in our group 15 mL (225 mg mepivacaine) was considerably shorter. Although differences in methodology preclude making direct comparisons, these observations may indicate that the reduction in block duration seen in our study is caused by the reduction in volume from 40 mL to 15 mL rather than the reduction in dose from 600 mg to 225 mg. However, further study is required to substantiate this. The data from our study are in accordance with the studies reporting a correlation between volume of local anesthetic and duration of peripheral nerve block.

The possibility of reducing the volume (and dose) of local anesthetic with ultrasound-guided peripheral nerve block is an obvious advantage from a safety perspective. Short- to intermediate-acting local anesthetics, such as mepivacaine, are used for surgeries where

postoperative pain is expected to be moderate and/or short lived. Block duration should cover surgery and the immediate period afterward, but prolonged analgesia postoperatively is not indispensable, and a reduction in block duration caused by reduced volume has little clinical relevance if surgery can be concluded before the block starts to wear off. Whether the pharmacodynamic findings regarding volume of mepivacaine equally apply for other local anesthetics, such as ropivacaine or levobupivacaine, remains to be determined. In situations where a long-acting local anesthetic is preferred, a shorter duration of sensory block may be an unfavorable trade-off when the intention is to obtain long-lasting postoperative analgesia. In those circumstances, the advantage of a dose reduction must be balanced against the possibility of a shorter duration of postoperative analgesia. In cases where prolonged postoperative analgesia is desirable, the use of a perineural catheter technique should be considered. Determining the lowest volume without decreasing duration of sensory block requires further study.

A limitation of our study is that we did not determine whether intraneural spread was present; although we tried to avoid intraneural injection, we cannot exclude the possibility that this may have occurred with individual nerves, which may have prolonged block duration.

In conclusion, reducing the volume of mepivacaine 1.5% for ABPB from 40 mL to 15 mL resulted in a reduction of overall block duration of approximately 17% to 19%, a reduction of block duration in individual nerves ranging from 18% to 40%, and a reduction in TTFR of approximately 30%.

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Chapter 03

Effect of local anesthetic concentration, dose and volume on the duration of single-injection ultrasound-guided axillary brachial plexus block with mepivacaine: a randomized controlled trial

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Abstract

Background: In what way volume, concentration and dose affect block duration is controversial. The purpose of the present study is to study the effect of dose, volume and concentration of mepivacaine on the duration of sensory and motor blockade in ultrasound-guided single shot axillary brachial plexus blockade.

Methods: In this parallel group randomized trial conducted in the Sint Maartenskliniek Nijmegen, 45 adult patients undergoing minor orthopaedic forearm, wrist or hand surgery were randomized to 3 groups. Group A: 20 mL mepivacaine 1.5%, Group B: 30 mL mepivacaine 1% and Group C: 30 mL mepivacaine 1.5%. Randomization was computer-generated, with allocation concealment by opaque sequentially numbered sealed envelopes. Patients and observers were blinded to group allocation. Primary outcome measure: duration of sensory block.

Results: Forty-five patients were randomized, four patients were excluded and replaced, and 15 patients in each group were included in the analysis. Mean (95% CI) sensory and motor block duration was 256 (230-282) and 254 (226-282) minutes in Group A, 226 (209-243) and 220 (200-240) minutes in Group B and 270 (249-291) and 264 (244-284) minutes in Group C. Duration of sensory and motor block duration differed significantly between groups (p=0.012 and p=0.016 respectively). Post-hoc analysis showed a significantly reduced sensory and motor block duration in Group B when compared to Group C of 44 min. No local anesthetic systematic toxity was reported.

Conclusions: When using equal volumes of mepivacaine for axillary brachial plexus block, a higher dose and concentration was associated with a longer duration of sensory and motor blockade, but not a higher volume.

Introduction

The introduction of ultrasound has changed the practice of peripheral nerve block (PNB). Using ultrasound guidance, local anesthetic (LA) spread around the nerves can be assessed with the possibility of repositioning the needle in case of maldistribution,[1] allowing for a reduction in LA dose without compromising the quality of PNB. Recent publications indeed illustrate that the volume of LA can be significantly reduced when particular regional anesthetic techniques are performed with ultrasound guidance.[2-5] While dose reduction is advantageous from a safety perspective, an unwanted tradeoff may be a shorter duration of the nerve blockade.

One of the factors affecting the duration of peripheral nerve block is the dose of LA, dose being the product of volume and concentration. In what way volume, concentration and dose of LA affect block duration is subject to debate.[6] In a recent study, we compared the duration of sensory and motor block of 15 and 40 mL mepivacaine 1.5% for axillary brachial plexus blockade (ABPB) using ultrasound guidance.[7] Volume reduction from 40 mL to 15 mL (62.5%) shortened the overall duration of sensory and motor block by approximately 17-19%, reduced sensory and motor block duration of individual nerves with 18-40% and decreased the time to first request of postoperative analgesia by approximately 30%. The difference in block duration observed in this study was the effect of either a reduction in volume from 40 to 15 mL or a reduction in dose from 600 to 225 mg or a combination. We designed the present study to determine if the reduction in duration of sensory and motor blockade in A is mainly affected by volume reduction or by dose reduction of mepivacaine. The null hypothesis was that sensory block duration is not affected by dose and volume reduction.

Materials and Methods

This study was set up as a Phase IV, monocenter, double-blinded (for observer and patient), parallel group randomized (1:1:1) trial. No protocol amendments were made during the study conduct. The study was approved by the Independent Review Board Nijmegen and was registered with the Nederlands Trial Register (www.trialregister.nl, number NTR3648) before onset of participant enrollment.

Eligible patients were all adults aged 18 or over with ASA physical health classification I-III, scheduled for single-injection ABPB for hand, wrist or forearm surgery. Exclusion criteria included contra-indications for regional anesthesia (infection at the injection site, coagulopathy), known hypersensitivity to amide-type local anesthetics, and known history of peripheral neuropathy. Specific criteria for withdrawal and replacement included: failure to perform adequate single-injection ABPB and failure to complete the study protocol. Patients were assessed for eligibility during the preoperative screening visit. Patients were informed about the study verbally and in writing and written informed consent was obtained from all patients.

The study was conducted at the Sint Maartenskliniek Nijmegen, The Netherlands between October 2012 and June 2014 according to the Declaration of Helsinki and later revisions thereof and in accordance with the ICH guidelines for Good Clinical Practice.

The Sint Maartenskliniek specializes in posture and movement. The orthopedic center is facilitated by an anesthesiology department specialized in locoregional and regional anesthesia techniques.

Study procedure

Study medication was prepared by an anesthetic nurse not involved in the study and was disclosed to the anesthesiologist performing the block procedure. Study medication consisted of either 20 mL mepivacaine 1.5%; 300 mg (Group A), 30 mL mepivacaine 1.0%; 300 mg (Group B), or 30 mL mepivacaine 1.5%; 450 mg (Group C).

After establishing intravenous access and routine monitoring (ECG, non-invasive blood pressure and peripheral oxygen saturation), ABPB was performed under ultrasound guidance using a short axis, in-plane technique. All blocks were placed by experienced anesthesiologists with the assistance of an anesthetic nurse. Blocks were performed under aseptic conditions using chlorexidine skin preparation and sterile ultrasound probe covers. The patient was placed in supine position with the head facing away from the arm to be blocked, the arm abducted and the elbow flexed in 90°. A 100-mm 22-gauge insulated short bevel needle (Stimuplex®; B. Braun, Melsungen, Germany) was inserted laterally in the axilla under ultrasound guidance. The musculocutaneous, median, ulnar and radial nerve were identified using ultrasound and the tip of the needle was brought in proximity of each individual nerve subsequently. The needle was connected to a nerve stimulator (Stimuplex® HNS 11; B. Braun) set to deliver 100 nC (0.1 ms, 1 mA) in order to facilitate identification of the individual nerves. The nerves were identified and blocked separately with one fourth of the study medication per nerve. Per patient one skin puncture was made, the needle was retracted subcutaneously and redirected under ultrasound guidance to approach the nerves individually. Time was designated t = 0 upon conclusion of the block procedure.

In case of insufficient analgesia at the surgical site at t = 30 min, an additional rescue block was placed in the block room, or surgery was performed under general anesthesia. These patients were excluded from further analysis and replaced.

Surgery was performed under regional anesthesia. In case of patient discomfort or upon patient request, sedation was provided with propofol (25–60 $\mu g.kg^{-1}.min^{-1}$) and remifentanil (0.01–0.04 $\mu g.kg^{-1}.min^{-1}$).

The patients received paracetamol 1g orally four times daily and etoricoxib 90 mg orally once a day, starting on the morning of surgery. When the block started to wear off, additional postoperative pain treatment consisted of morphine 0.1-0.15 mg/kg every 4h subcutaneously upon patient request.

Primary and secondary outcome measures

The primary outcome parameter was duration of sensory block. Secondary outcome parameters included duration of motor block, duration of sensory and motor block of individual nerves, block onset time, time to first request for additional postoperative pain treatment (TTFR) and patient satisfaction (NRS 0-10) with the anesthetic technique.

After injection of the local anesthetic solution, the onset of sensory and motor block was assessed every 5 min, until 30 min after injection. Sensory block of the medial antebrachial cutaneous, musculocutaneous, radial, median and ulnar nerves was assessed by pinprick. Sensory block was scored on a three-point scale as 0 = absent, 1 = partial and 2 = complete. At the same intervals, motor block of the musculocutaneous, radial, median and ulnar nerve was assessed (see Table 1) on a similar three-point scale (0 = no, 1 = partial and 2 = complete motor block). A complete overall sensory block was defined as a total score of 10; complete overall motor block was defined as a total score of 8.

Table 1. Baseline Characteristics

	Group A (n=15)	Group B (n=15)	Group C (n=15)
Sex, no. M/ no. F	2/13	6/9	7/8
Age (yr)	59±9	49±13	53±15
Height (cm)	165±7	172±8	171±11
Weight (kg)	71±13	75±7	78±17
ASA classification, no. 1/no. 2/ no. 3	3/10/2	10/5/0	7/8/0
Duration of surgery (min)	24±17	27±25	34±27
Site of surgery, no. left/ no. right	5/10	5/10	5/10
Type of surgery:			
- carpal tunnel release, no.	3	2	4
- trapezoidectomy, no.	6	1	2
- removement of osteosynthesis material, no.	2	4	1
- arthrodesis of finger, no.	0	2	1
- release trigger finger, no.	2	2	3
- arthrodesis of wrist, no.	0	1	2
- other, no.	2	3	2

Group A: 20 mL mepivacaine 1.5%. Group B: 30 mL mepivacaine 1.0%. Group C: 30 mL mepivacaine 1.5%. Values are absolute numbers, mean ± SD.

Upon arrival at the recovery, offset of sensory and motor block was assessed every 15 min in the same manner as preoperatively until full recovery. The primary outcome parameter was overall duration of sensory block defined as the time from t = 0 until the first postoperative measurement where total sensory score had returned to zero. Overall duration of motor block was defined as the time from t = 0 until the first postoperative measurement where total motor score had returned to zero. Block onset time was defined as the time from t = 0 until the time sensory respectively motor score was maximal. TTFR was defined as the time interval from t = 0 until the time the first request for postoperative analgesia was made.

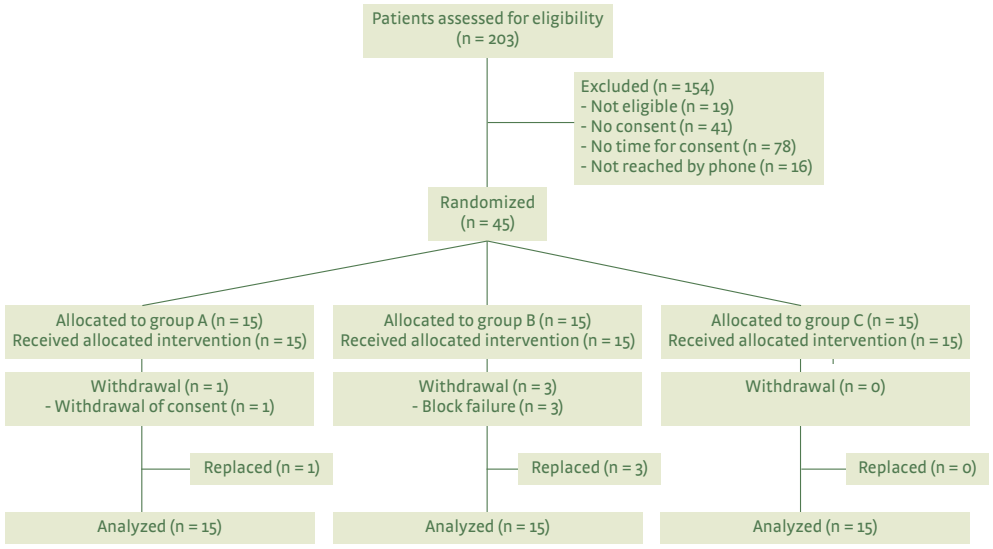

Fig. 1. Flowchart of patients enrolled in the study.

Sample size, randomization and blinding

The sample size calculation was similar to our previous study[7] and based on the overall duration of sensory block. In previous research, we[7], Bugamelli et al.[8], and Robaux et al.[9] found a variation (SD) in duration of sensory peripheral nerve block with mepivacaine of ± 47 min (47, 45 and 43 min respectively). Based on these data, the sample size required to have a 90% probability of detecting a difference of 60 min (approximately 25%) in duration of the ABPB between the groups (two sided, level of significance 0.05) is 13 patients per group. Compensating for variations in the standard deviation, we chose to include 15 patients per group. A computer-generated sequence of random numbers in 3 blocks of 15 and a 1:1:1 allocation was used for randomization. The allocation sequence was concealed from the researcher assessing and enrolling patients in sequentially numbered, sealed, opaque envelopes made by an independent researcher, not involved in the study.

A computerized database automatically assigned a study number to each patient assessed for eligibility. Once included in the study, the study number of the patient was written on the sealed randomization envelopes by the researcher. On the day of surgery the envelope was handed to an anesthetic nurse not involved in the study. The anesthetic nurse prepared the study medication according to the allocated group written on the card inside the envelope, wrote the study number of the patient on the card and resealed the envelope.

Patients with specific withdrawal criteria, as mentioned earlier in the methods section, were excluded and replaced. After 45 patients were included in the study, an independent researcher not involved in the study made additional sealed envelopes for the patients replacing the excluded patients, randomized and sequentially numbered to conceal treatment allocation for the observer.

At the conclusion of the study, all resealed envelopes were checked by an independent researcher not involved in the study, for any violations of the group allocation.

The anesthetic nurse that prepared the study medication was allowed to disclose allocation

to the anesthesiologist that performed the block procedure. Both patients and researcher were blinded for the volume and concentration of anesthetic solution used.

Statistical analysis

Per-protocol analysis was conducted using GraphPad Prism 6 software (GraphPad Software Inc, San Diego, CA).

For statistical comparison between the groups of overall sensory block (primary outcome parameter), motor block and the duration of individual nerve blocks one-way ANOVA analysis was used and Tukey post-hoc analyses were conducted. Block onset time and patient satisfaction (NRS 0-10) with the anesthetic technique was compared between groups with Kruskall Wallis test.

For between group comparison on baseline characteristics Chi square test and Kruskall Wallis test were used. All tests were 2-sided, and a p-value ≤ 0.05 was considered statistically significant. Frequency distribution was tested using Kolmogorov-Smirnov test for normality. Data are presented as mean (95% confidence interval) or median [range] as appropriate.

Results

In total, 45 patients were randomized, 15 patients per group. Four patients were excluded and replaced. Reasons for withdrawal were block failure (three patients in Group B) and patient consent withdrawal (one patient in Group A). All patients received the allocated intervention. A CONSORT flowchart is shown in Fig. 1. Baseline characteristics of the three groups did not differ significantly and are described in Table 1.

Thirty minutes after block placement, a complete sensory block was confirmed in 13 patients in Group A, 7 patients in Group B and 13 patients in Group C (p=0.006). Motor block was complete in 13 patients in Group A, 10 patients in Group B and 14 patients in Group C. Data on sensory and motor block scores of individual nerves after 30 min are shown in Table 2.

Table 2. Block Scores of Individual Nerves at 30 Minutes

	Group A (n = 15)			Group B (n = 15)			Group C (n = 15)		
Nerve	Score 2	Score 1	Score 0	Score 2	Score 1	Score 0	Score 2	Score 1	Score 0
Med. Anteb. Cut. sens	14	1	-	14	1	-	15	-	-
Musculocutaneous sens	13	2	-	14	1	-	15	-	-
Musculocutaneous mot	13	2	-	12	3	-	14	1	-
Radial sens	14	1	-	10	5	-	14	1	-
Radial mot	14	1	-	12	2	1	13	2	-
Median sens	14	1	-	12	3	-	15	-	-
Median mot	13	2	-	14	1	-	15	-	-
Ulnar sens	14	1	-	13	1	1	14	1	-
Ulnar mot	14	1	-	14	1	-	15	-	-

Group A: 20 mL mepivacaine 1.5%; Group B: 30 mL mepivacaine 1.0%; Group C: 30 mL mepivacaine 1.5%. Med. anteb. cut.: medial antebrachial cutaneous nerve; sens: sensory block score, mot: motor block score. Block was scored on a three-point scale as 0 = absent, 1 = partial and 2 = complete.

Sensory block, as well as motor block duration, differed significantly between groups: $p = 0.012$ and $p = 0.016$, respectively (Table 3). Post-hoc-between-group analyses showed a statistically shorter sensory and motor block duration of 44 min (20 %) in Group B when compared with Group C. Sensory and motor block duration in group A did not differ significantly from group B and C. Data on between-group differences of sensory and motor block duration are shown in Fig. 2 and Table 4.

Table 3. Duration of Axillary Plexus Nerve Block

Group A: 20 mL mepivacaine 1.5%; Group B: 30 mL mepivacaine 1.0%; Group C: 30 mL mepivacaïne 1.5%;

	Group A (n = 15)	Group B (n = 15)	Group C (n = 15)	*p*-value
Block duration (min)				
Overall sensory	256 ± 46 (186 – 363)	226 ± 31 (168- 274)	270 ± 39 (202 – 333)	**0.012**
Overall motor	254 ± 50 (186 – 363)	220 ± 36 (144 – 262)	264 ± 37 (202 – 305)	**0.016**
Block duration (min)				
Med. Anteb. Cut. nerve				
Sensory	222 ± 37 (165 – 292)	197 ± 42 (100 – 262)	247 ± 47 (118 – 303)	**0.010**
Musculocutaneous nerve				
Sensory	213 ± 40 (141 – 271)	196 ± 38 (144 – 262)	215 ± 53 (118 – 333)	0.446
Motor	224 ± 33 (165 – 277)	188 ± 43 (115 – 243)	216 ± 35 (171 – 296)	**0.031**
Radial nerve				
Sensory	228 ± 40 (180 – 307)	207 ± 23 (170 – 240)	227 ± 40 (185 – 295)	0.328*
Motor	229 ± 40 (165 – 307)	209 ± 35 (144 – 262)	258 ± 43 (202 – 305)	**0.003**
Median nerve				
Sensory	236 ± 44 (156 – 307)	204 ± 35 (145 – 251)	249 ± 43 (162 – 310)	**0.015**
Motor	245 ± 48 (156 – 322)	200 ± 42 (144 – 262)	241 ± 30 (195 – 295)	**0.015****
Ulnar nerve				
Sensory	238 ± 47 (186 – 363)	211 ± 40 (145 – 274)	249 ± 53 (133 – 310)	0.087
Motor	243 ± 57 (156 – 363)	209 ± 45 (144 – 262)	257 ± 37 (185 – 303)	**0.025**

med. anteb. cut. nerve: medial antebrachial cutaneous nerve. [a]no data because of a postoperative cast or bandage in 6 patients in Group A, 5 patients in Group B and 8 patients in Group C. [b]no data because of a postoperative cast or bandage in 3 patients in group A, 2 patients in Group B and 2 patients in Group C. Values are mean (95% CI). Bold data represent statistically significant differences

Table 4. Groupwise Comparisons of Block Duration

	Group A vs Group B		Group B vs Group C		Group A vs Group C	
	Difference (95% CI)	*p*-value	Difference (95% CI)	*p*-value	Difference (95% CI)	*p*-value
Block duration (min)						
Overall sensory	30 (-5 – 65)	0.100	**-44 (-79 – -9)**	**0.010**	-14 (-49 – 21)	0.599
Overall motor	34 (-3 – 70)	0.079	**-44 (-80 – -7)**	**0.017**	-10 (-47 – 27)	0.787
Block duration (min)						
Med. Anteb. Cut. nerve						
Sensory	24 (-13 – 62)	0.260	**-50 (-87 – -12)**	**0.007**	-25 (-63 – 12)	0.244
Musculocutaneous nerve						
Sensory	17 (-22 – 56)	0.550	-19 (-58 – 20)	0.482	-2 (-41 – 37)	0.993
Motor	**36 (2 – 69)**	**0.031**	-28 (-61 – 5)	0.110	7 (-26 – 41)	0.848
Radial nerve						
Sensory	22 (-18 – 61)	0.375	-21 (-63 – 22)	0.451	1 (-43 – 44)	0.999
Motor	20 (-13 – 52)	0.320	**-49 (-81 – -16)**	**0.002**	-29 (-62 – 3)	0.086
Median nerve						
Sensory	32 (-4 – 69)	0.091	**-44 (-80 – -8)**	**0.014**	-12 (-48 – 24)	0.709
Motor	**45 (5 – 84)**	**0.024**	**-41 (-79 – -2)**	**0.039**	4 (-35 – 44)	0.963
Ulnar nerve						
Sensory	27 (-15 – 70)	0.272	-38 (-80 – 4)	0.082	-11 (-53 – 32)	0.818
Motor	34 (-8 – 76)	0.137	**-48 (-91 – -6)**	**0.023**	-15 (-57 – 28)	0.684

Group A: 20 mL mepivacaine 1.5%. Group B: 30 mL mepivacaine 1.0%. Group C: 30 mL mepivacaine 1.5%; med. anteb. cut. nerve: medial antebrachial cutaneous nerve; CI: confidence interval. Values are calculated differences (95% confidence interval of the difference). Multiplicity adjusted *p*-values are given. Bold data represent statistically significant differenes

Because of the presence of a postoperative cast, offset of sensory block of the radial nerve could not be evaluated in 19 patients (6, 5 and 8 patients in Group A, B and C respectively). In these patients maximum postoperative sensory block score was 8 and overall sensory block duration was defined as the time until the total sensory score had returned to zero. The offset of motor block of the median nerve could not be tested in 7 patients (3, 2 and 2 patients in Group A, B and C respectively). In these patients maximum postoperative motor block score was 6 and overall motor block duration was defined as the time until the total motor score was returned to zero.

Only seven patients requested additional postoperative pain medication (four in Group A, one in Group B and two in Group C). Because of the limited number of data on TTFR, no average TTFR was calculated. Patient satisfaction with the anesthetic technique (NRS, on a scale 0 – 10) was comparable between Groups; 8.8±0.8 in Group A, 8.7 ± 1.7 in Group B and 8.9 ± 1.1 in Group C (p=0.76).

Twenty-eight patients received sedation upon request during surgery. In all included patients sensory block was adequate, none of the patients requiring conversion to general anesthesia. None of the patients showed signs or symptoms of local anesthetic systemic toxicity during the study procedure. In our hospital all patients are screened for postoperative nerve damage three weeks after surgery. None of the patients enrolled in the study expressed any sign of nerve damage at the postoperative screening.

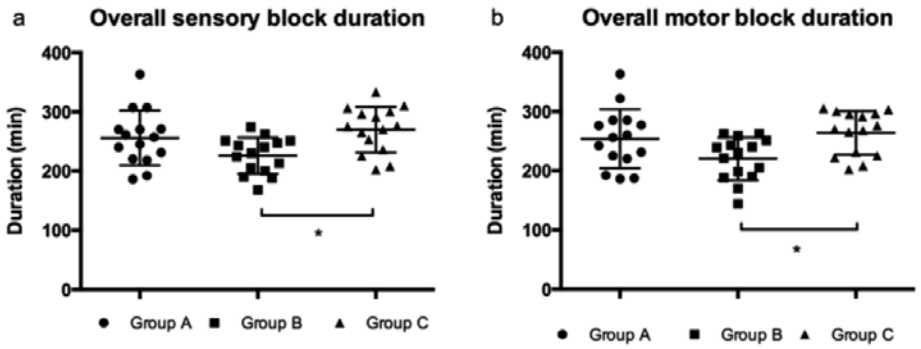

Fig. 2. Duration of overall sensory block (a) and overall motor block (b) per Group. Group A: 20 mL mepivacaine 1.5%. Group B: 30 mL mepivacaine 1.0%. Group C: 30 mL mepivacaine 1.5%.
Dots represent individual patients, the horizontal lines with error bars represent mean with SD. *p<0.05

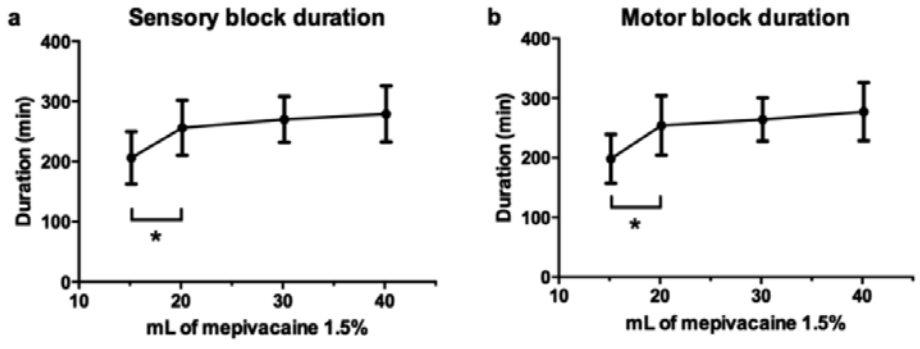

Fig. 3. Combined data on sensory block duration (a) and motor block duration (b) of the present study and 13 patients receiving 15 mL and 15 patients receiving 40 mL mepivacaine 1.5% from previously published work.[7]
Data are presented as mean with SD. *p<0.005

Discussion

Because of the inseparable relation between dose, volume and concentration, the issue which of these three entities is the major determinant of duration of nervous blockade is complex. In this study we compared the effects of equal doses in different volume/concentration, as well as different dose/concentration in equal volumes, and different volume/dose in equal concentrations of mepivacaine for ABPB in order to determine whether duration of sensory and motor blockade in is mainly affected by volume, concentration or dose.

Our results show that a higher dose and concentration administered results in a longer duration of sensory and motor block. When comparing the groups with equal concentrations in our study, no difference was found in block duration, despite the difference in dose and volume, suggesting a role for concentration and not for dose in determining block duration. When comparing the groups with equal dose, there is a tendency for a longer duration for sensory and motor block in the group with higher concentration and smaller volume. As it is unlikely that a smaller volume would explain this non-significant trend, this may indicate that concentration is proportional to the duration of nerve blockade when using equal doses. Serradell et al.[10] found no differences in the duration of analgesia when using 36 mL, 28 mL or 20 mL of mepivacaine 1% for ABPB, suggesting no relation between volume or dose and duration of analgesia. On the other hand, several others reported a direct relation between dose and duration,[7,11,12] although in these studies the higher doses were associated with higher volumes as well. Therefore it is unclear whether the effect is to be attributed to dose, volume or a combination of both. In a study using multivariate Cox regression to assess the effect of different volumes and concentrations of ropivacaine on the duration of analgesia following interscalene block for shoulder surgery, Fredrickson et al.[13] concluded that both volume and concentration affect duration independently.

In a previous study[7] comparing 40 mL and 15 mL mepivacaine 1.5% for ABPB, we reported that the volume/dose reduction of 62.5% resulted in a shorter overall duration of sensory and motor block of respectively 17% and 19%. In the present study we found that a dose reduction of 33% did not result in a reduction of block duration (Group A versus Group C). Although comparing results from different studies should be done with caution, the methodology of our present and previous study[7] is identical. Combining the observations from both studies, it seems that the relation between volume/dose and the duration of nervous blockade is not linear. Reducing the volume/dose of mepivacaine 1.5% from 600 mg (40 mL) to 300 mg (20 mL) results in a modest change in the median duration of nervous blockade of approximately 5%; a further decrease to 225 mg (15 mL) results in a decrease in duration of approximately 18% (Fig. 3). It seems therefore that in ABPB with mepivacaine 1.5%, the optimal balance between volume/dose reduction without significantly affecting duration of nervous blockade is 20 mL.

Three patients were excluded from the study because of block failure, all in Group B. While this may be due to the lower concentration of mepivacaine, our study was not set up nor powered to assess success rate of the different concentrations. In addition, from a clinical perspective, 1% mepivacaine may not be a suitable choice for ABPB, given the observed failure rate, the inferior onset characteristics, and the shortened duration.

In the patients randomized to group C we exceeded the maximum recommended dose of 4.5 mg/kg mepivacaine. Maximum recommended doses of local anesthetics are usually provided by the manufacturer with the obvious purpose of minimizing the incidence of systemic toxicity, but that does not mean that these recommendations are tantamount to safety.

On the contrary, maximum recommended doses are controversial because they are neither evidence based nor specific for site of injection or type of block.[14,15] In clinical practice larger doses are frequently used and it is our experience that 450 mg mepivacaine for axillary block in adult patients is well within the margin of safety.

A limitation of our study is that we were not able to collect postoperative data of all nerves in all patients because of the presence of a cast or a compression bandage. However, there were no significant differences in the duration of sensory and motor block between the different nerves within each group, with the exception of motor block duration of the musculocutaneous nerve in Group C, and we therefore think that the effect of the missing data on the conclusion of our paper is limited.

A second limitation is that our power analysis was based on a clinically relevant difference of 60 min, whereas in retrospect and from a scientific perspective smaller differences may also be interesting. The difference in duration between groups A and B is not statistically significant, but intriguing nevertheless and possibly a larger sample size would have unveiled a significant difference. Future research will focus on further investigating the effect of local anesthetic concentration on duration of sensory and motor block.

In conclusion, a decrease in volume from 30 to 20 mL mepivacaine does not influence block duration, but a higher dose and concentration in equal volumes of 30 mL results in a longer duration of sensory and motor block in ABPB.

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03

Chapter 04

Pharmacokinetics of 450 mg ropivacaine with and without epinephrine for combined femoral and sciatic nerve block in lower extremity surgery. A pilot study

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Abstract

Background: No pharmacokinetic data exist on doses of ropivacaine larger than 300 mg for peripheral nerve block in man, although in clinical practice higher doses are frequently used. The purpose of the present study was to describe the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine in patients undergoing anterior cruciate ligament reconstruction.

Methods: Twelve patients were randomly allocated to receive a single-shot combined sciatic/femoral nerve block with 60 mL of either ropivacaine 0.75% alone (group R, n = 6) or ropivacaine 0.75% plus epinephrine 5 μg mL^{-1} (group RE, n = 6). Venous blood samples for total and free ropivacaine serum concentrations were obtained during 48 hours following block placement. Pharmacokinetic parameters were calculated using a non-compartmental approach.

Results: Results are given as mean (SD) for group R vs. group RE. Total C_{max} was 2.81 (0.94) μg mL^{-1} versus 2.16 (0.21) μg mL^{-1} with a difference of 0.65 (95%CI -0.23–1.53). T_{max} was 1.17 (0.30) h vs. 1.67 (0.94) h with a difference of -0.50 (95%CI -1.40–0.40). AUC was 28.35 (5.92) μg h mL^{-1} vs. 29.12 (7.34) μg h mL^{-1} with a difference of -0.77 (95%CI -9.35–7.81). The highest free ropivacaine concentration per patient was 0.16 (0.08) μg mL^{-1} vs. 0.12 (0.04) μg mL^{-1}. $T_{1/2}$ was 6.82 (2.26) h vs. 5.48 (1.69) h.

Conclusions: Free serum concentrations of ropivacaine with and without epinephrine remained well below the assumed threshold of 0.56 μg mL^{-1} for systemic toxicity. With epinephrine coadministration, the peak concentrations tend to be lower and occur later. The AUC is equal in both groups.

Introduction

In recent years, peripheral nerve block (PNB) has rapidly gained popularity as an anesthetic technique for upper and lower extremity surgery. Compared to general anesthesia or central neuraxis blockade, interference of PNB with vital functions is minimal and postoperative analgesia is excellent.

For lower extremity surgery, a combination of two or three PNB's is usually necessary, especially when surgery is performed under exsanguination and the use of a tourniquet. With the combination of several PNB's, larger doses then recommended[1] are frequently used. Despite a plea for abandoning the practice of stating blanket maximum recommended doses for local anesthetics[2] and a widespread consensus that maximum recommended doses are not evidence-based, they continue to be mentioned in textbooks and by manufacturers. In the absence of pharmacokinetic data, using higher than recommended doses may pose a medico-legal problem in case of local anesthetic systemic toxicity.

Ropivacaine is a long-acting amide local aesthetic. It is structurally closely related to bupivacaine, but has a better safety profile with regard to central nervous system- and cardiotoxicity.[3] Unlike bupivacaine, which is a racemate, ropivacaine is a single S(-)-enantiomer.[4]

Several authors advocate the addition of epinephrine to large doses of local anesthetics in order to reduce the maximum concentration[1] or to act as a marker for intravascular injection.[5] However, the literature is inconclusive whether the addition of epinephrine 5 μg mL^{-1} (1:200,000) offers pharmacokinetic advantages over ropivacaine alone. Some studies did find an advantage,[3,6-8] whereas others did not.[9,10]

The purpose of the present study is to describe the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine, in patients undergoing anterior cruciate ligament reconstruction under single-shot combined sciatic/femoral nerve block.

Materials and Methods

Patients

This study was approved by the Independent Review Board Nijmegen and was registered at http://www.trialregister.nl (NTR1973) before onset of participant enrolment. Patients scheduled for anterior cruciate ligament repair were assessed for eligibility during the preoperative screening visit. Patients were informed about the study verbally and in writing and written informed consent was obtained from all patients. The study was conducted at the Sint Maartenskliniek Nijmegen, The Netherlands according to the Declaration of Helsinki and later revisions thereof and in accordance with the ICH guidelines for Good Clinical Practice.

Twelve patients (age 18 to 60 years, body weight >70 kg and ASA physical health classification I – III) were included. Exclusion criteria included contra-indications for regional anesthesia (infection at the injection site, coagulopathy), known hypersensitivity to amide-type local anesthetics, known history of peripheral neuropathy, known history of hepatic or renal insufficiency or use of fluvoxamine, ciprofloxacin, ketoconazole, erythromycin, clarithromycin, itraconazole, or rifampicin because of their effect on ropivacaine clearance.[1]

Anesthetic procedure

Using a computer-generated sequence of random numbers and a sealed envelope technique, patients were randomly allocated to receive a combined sciatic/femoral nerve block with 60 mL of either ropivacaine 0.75% (Naropin® AstraZeneca Sweden) alone (group R, n = 6) or ropivacaine 0.75% plus 5 µg mL^{-1} (1:200,000) epinephrine (group RE, n = 6). Blinded syringes containing the appropriate study solution were prepared by an anesthesia nurse not involved in the block procedure or the subsequent care of the patient. After establishing intravenous access and routine monitoring (ECG, non-invasive blood pressure and peripheral oxygen saturation), an indwelling venous catheter was placed in the contra lateral fossa cubiti for venous blood sampling.

The sciatic nerve block was carried out with the patient in the lateral decubitus position using the parasacral approach,[11] a 10 cm stimulating needle and a nerve stimulator. Upon request, the patients received mild sedation during the block procedure with 20 mg propofol i.v. and 0.5 mg alfentanil i.v. With the nerve stimulator set to deliver 100 nC (1 mA, 0.1 ms) at 2 Hz, the sciatic nerve was located by either plantar- or dorsiflexion of the foot. Needle position was optimized by reducing the current while maintaining the appropriate motor response, until the threshold was between 20 and 40 nC. After negative aspiration, 20 mL of local anesthetic was injected in the course of one minute in fractionated doses with intermittent aspiration after each 5 mL. Upon completion of the injection, time was designated as t = 0. Immediately following the sciatic nerve block the patient was turned supine and the femoral nerve block was performed with a 10 cm stimulating needle under ultrasound guidance using a short-axis view and an in-plane technique. As an additional aid to identify the femoral nerve, the needle was connected to a nerve stimulator set to deliver 100 nC (1 mA, 0.1 ms) at 2 Hz. Upon correct needle position as confirmed by ultrasound visualization and a motor response of the quadriceps muscle and after negative aspiration, 40 mL of local anesthetic was injected in the course of one minute in fractionated doses with intermittent aspiration after each 5 mL. A dose of 40 mL was chosen because it is our experience that this higher dose is associated with a higher incidence of complete 3-in-1 block. The total dose of both injections adds up to 450 mg ropivacaine with or without 300 µg epinephrine.

Surgery was performed under regional anesthesia. In case of patient discomfort or upon patient request, sedation was provided with propofol and remifentanil. There are no known interactions of the comedications used (propofol, alfentanil, remifentanil) with ropivacaine pharmacokinetics.[4]

Clinical assessments

During the first 120 min, patients were monitored and observed continuously for signs of systemic local anesthetic toxicity.

Sensory block was assessed 15 and 30 minutes after block placement in femoral and sciatic nerve supply areas. In case of inadequate anesthesia, intravenous sedation with propofol (25 – 60 µg kg^{-1} min^{-1}) and remifentanil (0.01 – 0.05 µg kg^{-1} min^{-1}) was initiated before surgical incision.

Blood sampling and assays

Venous blood samples of 5 mL were taken by the investigator (KS) before the first injection of local anesthetic (-0.25h), and at times 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12, 18, 24, 36 and 48 hours.

Samples were centrifuged within three hours of collection. Serum samples were stored at -40°C until assay. After determining total ropivacaine levels in serum, unbound ropivacaine levels were determined in ultra filtrate in 3 samples per patient: the sample with the highest total concentration as well as the samples taken immediately before and after. The highest concentration of these three measurements was taken as Cu_{max} for each individual patient.

Analysis of ropivacaine in serum and in ultra filtrate (free concentration) was performed by the Laboratory for Toxicology, Therapeutic Drug Monitoring and Pharmaceutical analysis of the Department of Hospital Pharmacy at the University Medical Center Groningen, Groningen, The Netherlands. A triple quadrupole Quantum LC/MS/MS system with a Surveyor MS pump and a Surveyor Plus autosampler (Thermo Scientific, Breda, the Netherlands) was used.

To obtain protein-free ultra filtrate, 300 µL serum was added to a Centrifree Ultra filtration device (Millipore, Amsterdam, the Netherlands) and centrifuged at 1000 g in a 33 ˚ fixed angle centrifuge for 10 minutes.

A 10 µL aliquot of serum or ultrafiltrate was transferred into an autosampler vial and 750 µL precipitation reagent (methanol 160 ml L^{-1}, ACN 840 ml L^{-1}, and cyanoimipramine 0.04 mg L^{-1}) with internal standard was added. The vials were then vortexed for 1 minute and stored at -20°C for 30 minutes to promote protein precipitation. The vials were centrifuged at 11,000 g for 5 minutes and 5 µL of the clear upper layer was injected onto a 50 x 2.1 mm HyPURITY Aquastar C18 analytical column (Interscience, Breda, The Netherlands). The mobile phase consisted of a gradient mixture of an acid buffer pH = 3.5 (containing ammonium acetate 5 g L^{-1}, acetic acid 35 mg L^{-1} and trifluoroacetic anhydride 2 mL L^{-1} of water), water and acetonitrile. Acetonitrile for LC-MS, trifluoroacetic anhydride for LC-MS, and water for LC-MS were purchased by BioSolve (Valkenswaard, The Netherlands). Methanol Lichrosolv and formic acid were from Merck KGaA (Darmstadt, Germany). Acetic acid 100%, ammonium acetate, ammonium formate (98-100%) were from Acros Organics (Geel, Belgium). All reagents were of suitable analytical grade. Ultra pure water was obtained from a Milli-Q water purifying system (Millipore Corporation, Billerica, MA, USA). The flow rate was 300 µL min^{-1}.

The mass selective detector was operated in electrospray-positive ionization mode and performed selected reaction monitoring. High purity nitrogen was used as the sheath gas and auxiliary gas, and argon was used as collision gas. Sample analysis was performed using the following transitions: ropivacaine m/z 275.0 > 126.2 (collision energy 22 eV) and the internal standard (cyanoimipramine) m/z 306.2 > 218.0 (collision energy 39 eV).

The LLOQ (Lower Limit of Quantification) of ropivacaine was set at 50 µg L^{-1} of serum (CV = 7.1%; n = 15) and 5 µg L^{-1} of ultra filtrate (CV = 6.8%; n = 15).

Pharmacokinetic analysis

Because of extravascular administration of ropivacaine at two different injection sites, a non-compartmental approach was used for the description of the ropivacaine pharmacokinetic parameters using MWPharm® (Medi-Ware BV, Zuidhorn, The Netherlands)[12]. Peak serum concentrations (C_{max}) and time to reach peak serum concentrations (t_{max}) were obtained directly from the measured serum concentration-time curves. The slope of the terminal log-linear portion of the serum concentration-time curve was determined by least-square regression to find the terminal elimination rate constant (λ_z). The terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration ($AUC(0,t_{last})$) was calculated using the linear trapezoidal rule. The area under the serum concentration-time curve from time zero to infinity ($AUC(0\text{-}\infty)$) was calculated as $AUC0\text{-}\infty = (AUC(0,t_{last})) + C_{last}/\lambda_z$. The Cu_{max} is the highest of three measured free ropivacaine concentrations per patient. The percent free concentration of ropivacaine was calculated as (Cu / total ropivacaine concentration in the corresponding sample) × 100%.

Sample size and statistics

The aim of this study was to describe the pharmacokinetic profile of 450 mg ropivacaine with and without epinephrine including the highest free ropivacaine concentrations. We decided to study two groups of six patients each. Randomization and blinding was performed to eliminate potential preference of anesthesiologists for the addition of epinephrine. The GraphPad InStat v.3.10 package (GraphPad Software Inc, San Diego, California) was used to perform descriptive statistics and to compare pharmacokinetic parameters using point estimates and 95% confidence intervals of the differences.
All data are presented as mean (SD) [range] or proportions.

Results

Twelve patients completed the study protocol, six in each group (Table 1).

Table 1. Patient Characteristics

	Group R	Group RE
Sex (M/F)	5/1	4/2
Age (yr)	27 (8)	31 (13)
Weight (kg)	90 (21)	81 (12)
Height (m)	1.82 (0.10)	1.77 (0.06)
BMI (kg m-2)	27 (3)	26 (3)

Group R: Ropivacaine 450 mg without epinephrine. Group RE: Ropivacaine 450 mg with epinephrine 5 µg mL^{-1}. Values are proportions or mean (SD).

Clinical outcome measures

Signs for systemic toxicity of local anesthetics were not observed.
The time to complete the femoral nerve block after completion of the sciatic nerve block was 6.2 (1.6) [3-8] minutes. Nine patients underwent surgery without need for additional sedation (five (R) and four (RE) patients), whereas three patients received sedation at any time during surgery due to patient discomfort (one (R) and two (RE) patients). Sedation was provided with a short acting sedative (propofol) and a short acting opioid drug (remifentanil) and was mild, patients maintaining spontaneous respiration at all times. None of the patients required conversion to general anesthesia.

Pharmacokinetics

Figures 1a and 1b show the individual and average concentration-time curves. Figure 2 shows these curves in detail during the first six hours. Total ropivacaine concentrations became < LLOQ (0.050 µg mL^{-1}) in all patients 35 – 50 hr after administration.

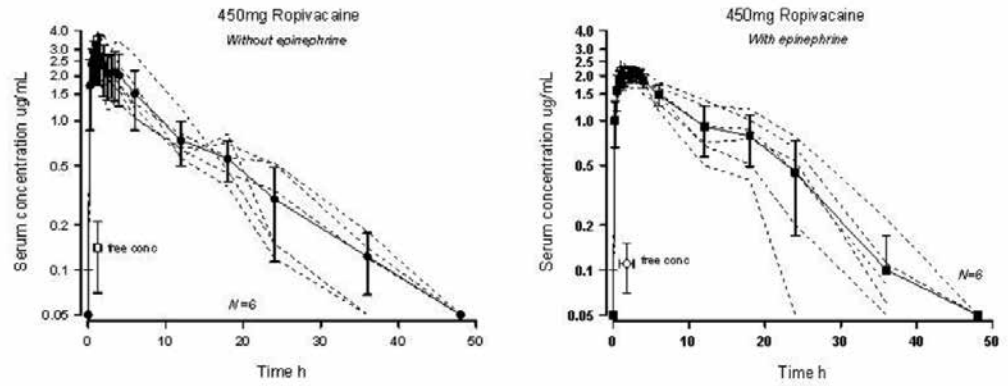

Fig. 1 a + b.
Individual (dotted lines) and mean with SD (solid lines) serum concentration-time curves of ropivacaine 450 mg without (fig.1a) and with epinephrine 5 µg mL^{-1} coadministration (fig.1b). Mean (SD), free concentration added. LLOQ = 0.050 µg mL^{-1}.

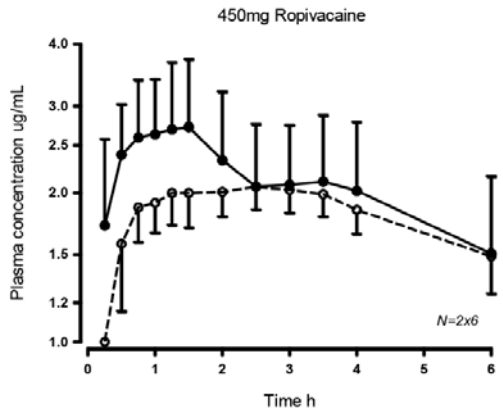

Fig. 2.
Mean (SD) serum concentration-time curves during the first 6 hours of ropivacaine without (solid dots) and with epinephrine coadministration (open dots). LLOQ = 0.050 µg mL^{-1}.

Table 2 shows data on C_{max}, t_{max} and other pharmacokinetic parameters, as well as the 95% confidence intervals for their differences. The measured maximum total concentration (Cmax) in group R was 2.81 (0.94) µg mL^{-1} and 2.16 (0.21) µg mL^{-1} in group RE. The 95% CI for the difference was from -0.23 to 1.52 µg mL^{-1} (p=0.13). The measured time to reach the maximum concentration (t_{max}) was 1.17 (0.3) h in group R versus 1.67 (0.94) h in group RE. The 95% CI for the difference was from -1.40 to 0.40 h (p=0.25). Elimination half-life ($t_{1/2}$) was 6.82 (2.26) h in group R and 5.48 (1.69) h in group RE.

Table 2. Pharmacokinetic Parameters.

	Group R	Group RE	Difference group R versus RE, (95% CI)
Cmax (µg mL-1)	2.81 (0.94) [1.94 – 3.82]	2.16 (0.21) [1.68 – 2.29]	0.65 (-0.23 – 1.53)
Tmax (h)	1.17 (0.30) [0.43 – 1.26]	1.67 (0.94) [1.25 – 3.35]	-0.50 (-1.40 – 0.40)
Cumax (µg mL-1)	0.16 (0.08) [0.07 – 0.30]	0.12 (0.04) [0.05 – 0.17]	0.04 (-0.04 – 0.12)
AUC (µg h mL-1)	28.35 (5.92) [22.49 – 39.23]	29.12 (7.34) [19.83 – 41.08]	-0.77 (-9.35 – 7.81)
T ½ (h)	6.82 (2.26) [4.71 – 9.73]	5.48 (1.69) [3.02 – 8.07]	1.34 (-1.23 – 3.91)

Groups as defined in Table 1. Values are mean (SD) [range]. C_{max} = maximum total ropivacaine concentration; T_{max} = time to C_{max}; Cu_{max} = maximum free ropivacaine concentration; AUC = area under the serum concentration-time curve from time zero to infinity; $T_{1/2}$ = elimination half-life.

Table 3 presents raw data on the highest free concentration per patient. The measured highest free ropivacaine concentration (Cu_{max}) was 0.16 (0.08) µg mL^{-1} in group R and 0.12 (0.04) µg mL^{-1} in group RE. The 95% CI for the difference was from -0.12 to 0.04 µg mL^{-1} (p=0.31). The percentage of free ropivacaine calculated from all samples was 5.1% (1.6) [2.2% to 8.0%] in group R and 5.2% (1.7) [2.4% to 8.5%] in group RE. Free ropivacaine concentrations are also shown in Figures 1a and 1b.

Table 3. Highest Measured Free Ropivacaine Serum Concentration per Patient and Corresponding Total Ropivacaine Serum Concentration.

Group R				Group RE			
Patient	Time (h)	Total conc. (µg mL^{-1})	Free conc. (µg mL^{-1})	Patient	Time (h)	Total conc. (µg mL^{-1})	Free conc. (µg mL^{-1})
2	1.5	4.09	0.21	1	1.5	1.99	0.17
3	1.25	1.75	0.14	4	0.75	2.33	0.15
5	0.75	2.25	0.13	6	1.5	1.79	0.09
8	1.0	2.10	0.07	7	1.25	2.12	0.05
9	1.25	2.40	0.13	10	3.0	2.10	0.14
11	1.5	3.89	0.30	12	1.25	2.37	0.14

Groups as defined in Table 1. Time points are at Cu_{max}.

Discussion

This is the first study describing the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine for combined sciatic/femoral nerve block.

In the current literature, several studies report pharmacokinetic data on ropivacaine doses of 300 mg. Cuvillon and colleagues[13] and Vanterpool and colleagues[14] used 300 mg ropivacaine with epinephrine (1:200,000 and 1:400,000 respectively) in combined lumbar plexus/sciatic nerve block and found a C_{max} for total ropivacaine of 1.84 (0.59) µg mL^{-1} and 1.56 (0.35) µg mL^{-1} respectively and a t_{max} less than 1 hour. In these studies, samples were only taken until 90 min[13] and 4 h[14] after injection and therefore they do not provide data on elimination half-lives. Wank and colleagues[15] and Pere and colleagues[16] studied the pharmacokinetic profile of 300 mg ropivacaine without epinephrine in axillary brachial plexus block and found a C_{max} of 2.3 (0.8) µg mL^{-1} and 1.8 (0.5) µg mL^{-1} respectively. In both studies, t_{max} was less than 1 hour and elimination half-lives were 6.1 (1.8) h[15] and 8.4 (10.5) h[16]. Although these studies differ from ours with respect to dose and site of injection, the t_{max} and $t_{1/2}$ are comparable to the data obtained in our group R (t_{max} = 1.17 (0.3) h; $t_{1/2}$ = 6.82 (2.26) h).

The major concern when using high doses of local anesthetic is systemic toxicity. If and when systemic toxicity occurs, depends on the free ropivacaine serum concentration exceeding the toxic threshold. Ropivacaine in serum is mainly bound to α1-acid glycoprotein (AAG) and the percent free concentration is approximately 6%.[17] In a study in healthy volunteers receiving iv. ropivacaine, Knudsen and colleagues[18] defined the toxic threshold for free ropivacaine in arterial samples as 0.56 [range: 0.34 – 0.85] µg mL^{-1}. In our study we took venous samples; however, when absorption into the central compartment is slow (as is the case with perineural injection), arterial and venous concentrations will be comparable. The highest free ropivacaine serum concentration we found in our study remains well below the threshold of 0.56 µg mL^{-1}. Systemic toxicity may occur directly in relation with the injection of local anesthetic, or after a delay. Direct systemic toxicity occurs in case of accidental intravenous injection; serum concentration rises rapidly and the interval between injection and the onset of symptoms is characteristically short (1-2 min). Excluding accidental intravenous injection, the free ropivacaine serum concentration may still rise above the toxic threshold and result in systemic toxicity. In the latter case, the concentration-time profile is determined by total dose and absorption from the site of injection into the central compartment, as well as by distribution and elimination. In this case, the delay between the injection and the onset of symptoms is much longer (>15 min).

A limitation of the present study is the small numbers in each group. Our study groups contained six patients each and authorative statements about safety obviously require larger numbers. However, in the past 10 years, more than 5,000 patients at our institution have received a combined sciatic/femoral nerve block with 450 mg of ropivacaine. During this period, we have observed only one patient with mild signs of delayed systemic toxicity (anxiety and restlessness, 45 min after injection) that resolved within minutes without treatment.

A second limitation of this study is the relatively high total dose of ropivacaine. With the introduction of ultrasound, there has been a rapid refinement in block placement techniques. The use of ultrasound allows a reduction in local anesthetic volume and dose without compromising block efficacy, reducing the need for large doses as described in this study. However, doses exceeding the maximum recommended dose of 300 mg ropivacaine still occur regularly. As such there remains a need for pharmacokinetic data on doses of ropivacaine for peripheral nerve block that are higher than the maximum recommended dose.

The rationale for adding epinephrine to reduce the maximum plasma concentration is local vasoconstriction at the site of injection[19] thereby slowing absorption. Several studies found a decrease in C_{max} and an increase in t_{max} as a result of adding epinephrine to ropivacaine for epidural,[7,8] caudal[20] or regional[6] (thoracic paravertebral block) anesthesia. On the other hand, for perivascular subclavian block, Hickey et al.[9] found no effect on pharmacokinetics (C_{max}, t_{max} or AUC) after the addition of epinephrine to ropivacaine.
In our study, the peak concentrations tend to be lower and occur later with epinephrine coadministration. The AUC is equal in both groups.
To document the pharmacokinetic safety of higher than recommended doses of ropivacaine, as well as to study the effect of adding epinephrine, adequately powered studies are necessary. The results of this study may serve as a basis for such studies.
In conclusion, this is the first study describing the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine for combined sciatic/femoral nerve block. Free serum concentrations of ropivacaine in both groups remained well below the assumed threshold of 0.56 µg mL^{-1} for systemic toxicity.

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Chapter 05

The effects of adding epinephrine to ropivacaine for popliteal nerve block on the duration of postoperative analgesia: a randomized controlled trial

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Abstract

Background: Duration of peripheral nerve blocks depends on multiple factors. Both technique and type of local anesthetic used, either with or without adjuncts, may result in different duration times of the block. The purpose of the present study was to compare the duration of postoperative analgesia of 30 mL ropivacaine 0.75% with or without epinephrine for popliteal sciatic nerve block.

Methods: Thirty-eight patients were included to receive ultrasound guided continuous popliteal nerve block with ropivacaine 0.75% either without (ROPI) or with epinephrine 5 µg/mL (ROPI-EPI) for ankle fusion, subtalar fusion, or a combination of both. The primary outcome parameter was the duration of postoperative analgesia as reflected by the time to first request for postoperative analgesia (TTFR) through the popliteal nerve catheter. Secondary outcome measures included the onset of sensory and motor block and NRS score for pain at rest and during movement.

Results: Thirty patients, 15 in each group, were studied. Eight patients were withdrawn because of specific withdrawal criteria described in the protocol and replaced according to their group allocation. Median [interquartile range] TTFR was 463 [300-1197] min and 830 [397-1128] min for the ROPI vs ROPI-EPI group respectively. Hodges Lehman median difference between groups was 71 min (95% CI: -415 – 473 min). There was no difference in any clinical outcome measure between the groups.

Conclusions: The results of this study did not show any significant increase in the duration of postoperative analgesia by adding epinephrine to ropivacaine for popliteal nerve block. This may be due to the intrinsic vasoconstrictive properties of ropivacaine. The absence of a significant difference can also be the result of a type II error caused by a large variation in the individual TTFR.

Introduction

Duration of peripheral nerve block depends on several factors such as the choice of local anesthetic (LA), the site of injection and the presence of adjuncts such as clonidine or epinephrine. Epinephrine may be added to (large) doses of local anesthetics (LA) with the objective to reduce the maximum plasma concentration[1] or to act as a marker for inadvertent intravascular injection.[2] The rationale for adding epinephrine to reduce the maximum plasma concentration is local vasoconstriction at the site of injection,[3] thereby slowing absorption. A decrease in absorption increases the duration of analgesia.[4] The literature however, is inconclusive regarding this effect. Several studies find a decrease in C_{max} and an increase in t_{max} as result of adding epinephrine to ropivacaine for epidural,[5,6] caudal[7] or regional[8] (thoracic paravertebral block) anesthesia confirming a decrease in absorption. However, others fail to confirm prolonged sensory block duration when adding epinephrine to ropivacaine.[9,10] In a recent study aimed to describe the pharmacokinetic profile of high dose ropivacaine with and without epinephrine,[11] we found an indication of prolonged time to first request for postoperative analgesia (TTFR) after the addition of epinephrine to ropivacaine for combined sciatic/femoral nerve block for anterior cruciate ligament reconstruction. In this study of 12 patients,[11] 3 did not request postoperative analgesia (1 in the ROPI-group and 2 in the ROPI-EPI-group). For the remaining patients the median TTFR was 17 [12.5-22] h in the ROPI-EPI-group and 3.5 [3-17] h in the ROPI-group. Because of the small number of patients, these data have not been included in the original publication.

The purpose of the present study is to compare the duration of postoperative analgesia of 30 mL ropivacaine 0.75% with or without epinephrine for popliteal sciatic nerve block.

Materials and Methods

Patients

This prospective double blinded (for observer and patient) randomized study was approved by the Independent Review Board Nijmegen (protocol number NL39628.072.12, date of approval 28-02-2012) and was registered at http://www.trialregister.nl (NTR3330, keyword TTFR) before onset of participant enrolment. The study was conducted at the Sint Maartenskliniek Nijmegen, The Netherlands according to the Declaration of Helsinki and later revisions thereof and in accordance with the ICH guidelines for Good Clinical Practice. Patients scheduled for continuous popliteal sciatic nerve block for ankle fusion, subtalar fusion, or a combination of both were assessed for eligibility during the preoperative screening visit. Patients were informed about the study verbally and in writing and written informed consent was obtained from all patients. Eligible participants were all adults aged 18 or over with ASA physical health classification I-III. Exclusion criteria included contra-indications for regional anesthesia (infection at the injection site, coagulopathy), known hypersensitivity to amide-type local anesthetics, known history of peripheral neuropathy, inability to understand numerical pain scales, and inability to operate a Patient-Controlled Analgesia (PCA) device. Specific criteria for withdrawal (and replacement) included: failure to perform adequate continuous popliteal sciatic nerve block; pain in the distribution of the sciatic nerve upon arrival at the recovery directly postoperatively requiring a therapeutic intervention (block failure); and failure to complete the study protocol (e.g. no request for postoperative analgesia).

Anesthetic procedure

All patients received paracetamol 1000 mg orally three times daily and etoricoxib 90 mg orally once a day, starting on the morning of surgery for at least 7 days. Intravenous access and routine monitoring were established in all patients. According to a computer-generated sequence of random numbers and a sealed envelope technique, patients received continuous popliteal nerve block with ropivacaine 0.75% either without (ROPI, n = 15) or with epinephrine 5 µg/mL (ROPI-EPI, n = 15). All popliteal blocks were placed with the patient in the lateral decubitus position on the non-dependent side using ultrasound guidance and a posterolateral in-plane approach. A nerve stimulator set to deliver 100 nC (1 mA, 0.1 ms) at 2 Hz was used as an additional aid. The tibial, peroneal and sciatic nerves were identified and injection was made at the level of the bifurcation of the sciatic nerve. Thirty mL ropivacaine 0.75% without or with epinephrine 5 µg/mL was injected in fractionated doses. Time was designated t = 0 upon conclusion of the popliteal sciatic nerve block. A perineural catheter was inserted through the needle after injection of the loading dose. Upon completion of the popliteal nerve block the patient was placed in the supine horizontal position. Because surgery was performed under exsanguination and a tourniquet, a single shot ultrasound-guided femoral or saphenous nerve block with 20 mL mepivacaine was performed to facilitate the use of the tourniquet. Surgery was performed under regional anesthesia alone, or supplemented with sedation upon patient request. If the planned duration of surgery exceeded 120 min, patients received general anesthesia with propofol, remifentanil and a laryngeal mask.

Upon arrival at the recovery room, a PCA-pump (GemStar®, Hospira Inc. Lake Forest, Illinois, USA) was connected to the popliteal catheter set up to deliver bolus doses of 10 mL ropivacaine 0.2%, with a lock-out time of 15 minutes, no background infusion and a maximum of 30 mL per 4 hours. The intensity of postoperative pain was evaluated by Numeric Rating Scale (NRS, 0-10). Prior to surgery, patients had been instructed to use the PCA device to maintain postoperative pain scores at or below NRS 3.

Clinical assessments

Baseline characteristics of participating patients were recorded (i.e. age, length and weight). During the first 45 minutes after performance of the popliteal nerve block, a blinded observer assessed the onset of sensory and motor block every 5 minutes until complete block of the tibial and peroneal nerve. Sensory block of the tibial and peroneal nerves was assessed by pinprick at the heel of the foot (tibial nerve) and dorsum of the foot between the 1st and 2nd toe (peroneal nerve). Sensory block was scored on a three-point scale as 0 = absent, 1 = partial and 2 = complete. Motor function of the tibial (plantar flexion foot) and peroneal nerve (dorsal flexion of foot) were also assessed on a three-point scale with 0 = no motor block, 1 = partial and 2 = complete motor block. Complete sensory and motor block was defined as a total score of 8. In those patients that did not have a complete block before the beginning of surgery, we assessed block success upon arrival at the recovery room directly postoperatively. In these patients, block success was defined as absence of pain requiring therapy in the distribution of the sciatic nerve distribution area, while patients requiring pain relief were deemed failures and were excluded from the study. Type and duration of surgery were recorded. At t = 24h the PCA pump was read out and the TTFR was noted. TTFR was defined as the time from t = 0 until the time that the patient made the first request for analgesia via the PCA pump. In case no request had been made, sensory and motor block were evaluated in the same manner as preoperatively, and ropivacaine consumption was checked again at t = 48h.

The primary outcome parameter was the duration of postoperative analgesia as reflected by the TTFR. Secondary outcome measures included the onset of sensory and motor block, NRS score for pain at rest and during movement directly postoperatively, at t = 24h and if necessary at t = 48h and satisfaction score (NRS 0-10) with the anesthetic technique at the time of completion of the study.

Sample size and statistical analysis

Taboada et al.[12] have reported a duration of 19 ± 3.4 h postoperative analgesia after popliteal block with 30 mL ropivacaine 0.75%. Based on these data, the sample size required to have an 80% probability of detecting a difference of 20% (two-sided, level of significance 0.05) in the duration of postoperative analgesia between the groups was 12 patients per group. We chose to include 15 patients per group to compensate for variation in standard deviation. Patients with specific withdrawal criteria, as mentioned earlier in the methods section, were withdrawn and replaced. An independent monitor not involved in further conduction of the study made new sealed envelopes according to group allocation of the withdrawn patients. Data were analyzed using the GraphPad Prism 6 software (GraphPad Software Inc, San Diego, CA). Analysis was per protocol. The D'Agostino & Pearson omnibus normality test was used for normality testing. Continuous, normally distributed data are presented as mean ± SD [range], non-normally distributed data as median [interquartile range]. For statistical comparison between the groups, the student-t test for normally distributed data and the Mann Whitney U test for nonparametric comparisons was used. In case a parameter is normally distributed in one group and non-normally in the other group, the data are presented as median [interquartile range] and a nonparametric test used for statistical comparison. The Hodges-Lehmann estimate was used for calculating the difference between population medians with 95% CI; the difference between each value in the ROPI group and each value in the ROPI-EPI group was computed and the Hodges-Lehmann estimate is the median of this set of differences. The part of patients without need for postoperative analgesia in group ROPI vs. ROPI-EPI were compared using Chi squared test. A p-value < 0.05 was considered statistically significant.

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Results

In order to study 15 patients in each group, 38 patients were included in the study protocol between July 2012 and March 2013. A Consort flowchart is shown in Figure 1. Five patients in the ROPI group and three in the ROPI-EPI group were withdrawn on account of specific withdrawal criteria described in the protocol. These included failure to complete the study protocol (i.e. no request for postoperative analgesia at t = 48 h; one in each group, and no preoperative block assessment; also one in each group) and pain requiring therapy in the distribution of the sciatic nerve upon arrival at the recovery directly postoperatively (block failure; three in the ROPI group, one in the ROPI-EPI group). There were no significant differences in patient characteristics between the two groups (Table 1).

Table 1. Patient Characteristics

	ROPI	ROPI-EPI
Sex (M/F)	8/7	9/6
Age (yr)	61 ± 7	56 ±11
Length (cm)	177 ± 12	175 ± 8
BMI (kg/m2)	28 ± 4	30 ± 5
ASA (I/II/III)	4/10/1	5/10/0
Surgery	Ankle fusion: 9 (1) Subtalar fusion: 6 Combination: 0	Ankle fusion: 10 (3) Subtalar fusion: 4 (1) Combination: 1
Operation time (min)	87 ± 33	92 ± 33

ROPI: popliteal block with 30 mL ropivacaine 0.75% without epinephrine; ROPI-EPI: popliteal block with 30 mL ropivacaine 0.75% with epinephrine 5 µg/mL. Values are proportions, mean ± SD or actual numbers. Differences between the groups were not significant. *Patients with medial incision beside lateral incision.

Due to OR logistics, block onset could not be measured at 45 minutes in all patients. In case a patient did not have a complete block before the beginning of surgery, block success or failure was defined as absence or presence of pain requiring therapy in the distribution of the sciatic nerve upon arrival at the recovery directly postoperatively. Patients with a failed block were excluded and replaced, patients with a successful block remained in study. Table 2 shows sensory and motor block onset scores for patients with a successful block upon arrival at the recovery.

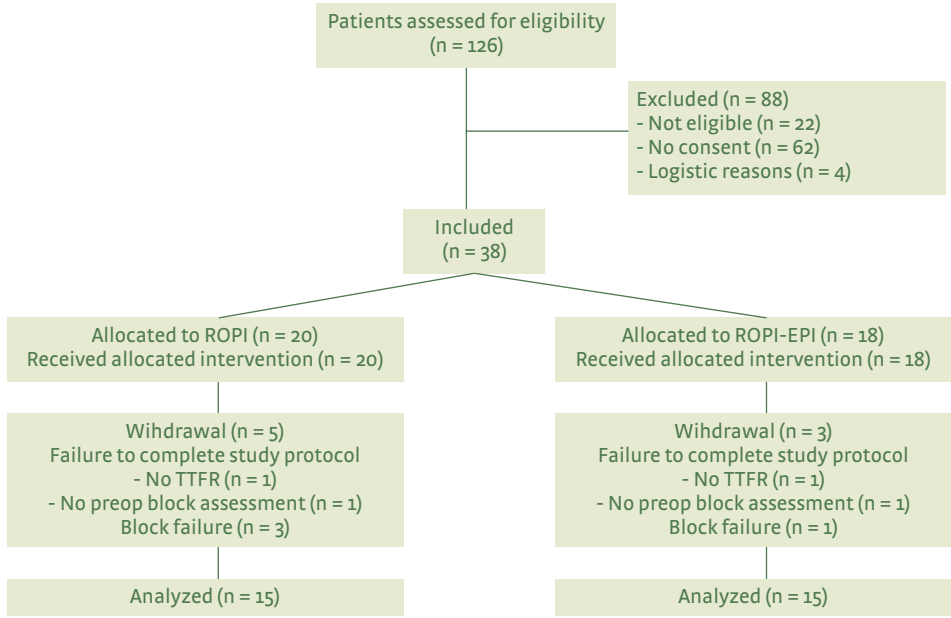

Fig. 1. Consort flowchart of patients enrolled in the study

Table 2. Onset Scores of Individual Nerves at Beginning of Surgery

Nerve	ROPI			ROPI-EPI		
	Complete	Partial	Absent	Complete	Partial	Absent
Tibial sensory	4	11	1	9	4	2
Tibial motor	10	3	2	9	5	1
Peroneal sensory	12	3	-	11	4	-
Peroneal motor	11	2	2	10	3	2

Groups as defined in Table 1. Values represent numbers of patients.

Figure 2 shows individual TTFR data points for both groups. Median [IQR] time to first request for postoperative analgesia was 463 [300-1197] min and 830 [397-1128] min for the ROPI vs. ROPI-EPI group respectively. Hodges Lehman median difference between groups was 71 min (95% CI: -415 – 473) for the ROPI-EPI vs. ROPI group. There were no differences in any clinical outcome measures between the groups (Table 3).

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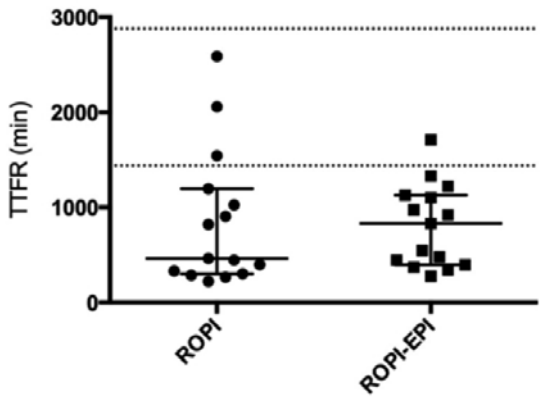

Fig. 2. Individual data points of time to first request for postoperative analgesia
ROPI: popliteal block with 30 mL ropivacaine 0.75% without epinephrine; ROPI-EPI: popliteal block with 30 mL ropivacaine 0.75% with epinephrine 5 µg/mL; TTFR: Time To First Request for postoperative analgesia. Horizontal lines represent medians ± interquartile range.
Dotted lines represent t = 24 and 48 hours.

Table 3. Clinical Outcome Measures

	ROPI	ROPI-EPI	*p*-value
TTFR (min)	463 [300-1197]	830 [397-1128]	0.56
NRS rest at t=24h	1 [0-3]	1 [1-3]	0.70
NRS movement at t=24h	1.5 [0-3]	2 [1-3]	0.47
NRS max during 24 h	4 [2-7]	6 [3-8]	0.17
NRS satisfaction with block	8 [8-9]	9 [8-10]	0.08

Groups as defined in Table 1. Values are median [IQR]. TTFR: Time To First Request for postoperative analgesia; NRS: Numeric Rating Scores (0-10)

Discussion

The results of this study did not show a significant increase in the duration of postoperative analgesia by adding epinephrine to ropivacaine for popliteal nerve block.
A prolonged duration of postoperative analgesia by adding epinephrine to ropivacaine was expected based on our clinical experience. In a previous study, we found an indication of prolonged TTFR after the addition of epinephrine 5 µg/mL to 450 mg ropivacaine for combined sciatic/femoral nerve block for anterior cruciate ligament reconstruction.[11]
However this study was underpowered to make comparisons in TTFR. In the present study we were unable to confirm this expected difference in sensory block duration. Although the difference in the median TTFR between the groups is large (367 min), the data show a large variation and data in group ROPI are skewed with a long tail and therefore are not normally distributed. The Hodges Lehman estimate of the median difference was 71 min (95% CI: -415 – 473). As a result of the large variation in our data the risk of a type II error is considerable. The absence of a statistically significant difference should therefore be interpreted with caution.
Our results are consistent with previous findings by Cederholm[9] and Weber[10]. Cederholm found no difference in duration of sensory block during epidural analgesia with 20 mL ropivacaine 0.5% or 0.75% either with or without epinephrine 5 µg/mL. Weber did not find an effect of epinephrine 5 µg/mL added to 20 mL ropivacaine 0.5% and 0.2% on postoperative analgesia via a femoral catheter after total knee replacement.
Epinephrine is thought to prolong block duration based on a decrease in local anesthetic absorption due to local vasoconstriction at the site of injection.[3] Ropivacaine has intrinsic vasoconstrictive properties. Cederholm[13] found an inverse dose-response relationship in which the weakest solutions of ropivacaine (0.063% and 0.125%) showed the most marked reduction in skin blood flow measured by laser doppler as compared to normal saline. Kopacz[14] found that subcutaneous injection of ropivacaine 0.25% and 0.75% reduced cutaneous blood flow in pigs to a similar degree at both concentrations also measured by laser doppler. The addition of epinephrine to ropivacaine did not alter the maximum decrease in blood flow observed; however epinephrine significantly decreased blood flow when added to saline.
This quality of ropivacaine may also explain the absence of a clinical significant difference in block duration of ropivacaine either with or without epinephrine found in our study.
Our study has several limitations. We did not measure block duration by assessing sensory and motor block at regular time intervals, and TTFR is a subjective measure of block duration. However, pinprick assessments of sensory block during 24-48h, including night-time, is bothersome for patients and, for instance, in the present study impossible due to the post-operative cast management. From a clinical perspective duration of analgesia is more important than duration of sensory block. We therefore feel that using the TTFR as a tool to measure block duration is acceptable.Our decision to replace the two patients (one in each group) who made no request for pain relief during 48 h and in whom there were no longer signs of sensory sciatic nerve bock is debatable, as it may be argued that both patients had a successful sciatic nerve lock. However, since the primary outcome parameter (TTFR) was absent in these patients and the sciatic nerve block had worn off, we felt it would have been inappropriate to censor these data to 48 h and include them in the analysis.

Furthermore, anesthesiologists were not blinded for treatment allocation. All block were performed by experienced anesthesiologists in a standardized fashion as described in the treatment protocol. Since they were not involved in block assessment or in any other way in the conduction of the study, we believe that the absence of blinding of the anesthesiologists performing the blocks does not affect the results.
Another limitation is that we studied the duration of analgesia of the popliteal nerve block for ankle fusion surgery while the cutaneous sensory supply of the medial malleolus is by the saphenous nerve. Clendenen and Whalen histologically verified that the saphenous nerve innervates not only the skin, but also the periosteum of the medial malleolus and joint capsule.[15] Because we performed only a single-shot femoral or saphenous nerve block with mepivacaine, the TTFR in individual patients may have been triggered by pain in the distribution of the saphenous nerve, and thus reflect the duration of sensory block of the femoral or saphenous nerve rather than the sciatic nerve. Standard incision for ankle fusion and subtalar fusion is on the lateral side. However, an additional medial incision was made in 5/30 patients. In four of these patients the TTFR was > 360 min. Because the duration of sensory femoral or saphenous nerve block is shorter, we believe that the effect of pain in the distribution of the saphenous nerve on the TTFR is minimal.
In conclusion, we were unable to confirm an expected difference in the duration of postoperative analgesia by adding epinephrine to ropivacaine for popliteal nerve block. This may be explained on the basis of the intrinsic vasoconstrictive properties of ropivacaine or due to a large variation in the individual TTFR, the absence of a significant difference may also be caused by a type II error.

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Chapter 06

No correlation between minimal electrical charge at the tip of the stimulating catheter and the efficacy of the peripheral nerve block catheter for brachial plexus block: a prospective blinded cohort study

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*BMC Anesthesiology 2014 Apr 11;**14**:26*

Abstract

Background: Stimulating catheters offer the possibility of delivering an electrical charge via the tip of the catheter. This may be advantageous as it allows verifying if the catheter tip is in close proximity to the target nerve, thereby increasing catheter performance.
This prospective blinded cohort study was designed to investigate whether there is a correlation between the minimal electrical charge at the tip of the stimulating catheter, and the efficacy of the peripheral nerve block (PNB) catheter as determined by 24h postoperative morphine consumption.

Methods: Forty adult patients with ASA physical health classification I-III scheduled for upper extremity surgery under combined continuous interscalene block and general anesthesia were studied. Six patients were excluded from analysis.
After inserting a stimulating catheter as if it were a non-stimulating catheter for 2-5 cm through the needle, the minimal electrical charge necessary to obtain an appropriate motor response was determined. A loading dose of 20 mL 0.75% ropivacaine was then administered, and postoperative analgesia was provided by a continuous infusion of ropivacaine 0.2% 8 $mL.h^{-1}$ via the brachial plexus catheter, and an intravenous morphine patient-controlled analgesia (PCA) device.
Main outcome measures include the minimal electrical charge (MEC) at the tip of the stimulating catheter necessary to elicit an appropriate motor response, and the efficacy of the PNB catheter as determined by 24h postoperative PCA morphine consumption.

Results: Mean (SD) [range] MEC at the tip of the stimulating catheter was 589 (1414) [30 – 5000] nC. Mean (SD) [range] 24h morphine consumption was 8.9 (9.9) [0-29] mg. The correlation between the MEC and 24h postoperative morphine consumption was Spearman's Rho r_s = -0.26, 95% CI -0.56 to 0.09.

Conclusion: We conclude that there is no proportional relation between MEC at the tip of the blindly inserted stimulating catheter and 24 h postoperative morphine consumption.

Introduction

Peripheral nerve block (PNB) is popular among anesthesiologists and patients for peri- and postoperative pain relief. PNB can be administered as a single shot or continuously using a catheter. For continuous PNB, non-stimulating and stimulating catheters are available. Non-stimulating catheters are inserted blindly through the needle after obtaining a correct needle position as determined by nerve stimulation (NS) and/or ultrasound. Because catheters are usually inserted some distance beyond the needle tip to avoid inadvertent dislocation, verifying a correct catheter position is not possible. Therefore, most anesthesiologists choose to administer a loading dose through the needle before placing the catheter. Whether the catheter tip is correctly placed does not become apparent until after the effect of the loading dose has worn off, usually late at night.
The use of ultrasound has become state of the art for PNB to ensure close proximity of the needle tip to the nerve before injecting the local anesthetic. Nevertheless, nerve stimulation is still widely used as the sole technique or to double-check needle position. Although there is no predefined relationship between the minimal electrical charge necessary to elicit an appropriate motor response, i.e. a contraction of a muscle innervated by the stimulated nerve (MEC), and the actual distance of the needle tip to the target nerve, it is generally assumed that the MEC has to be below 50 nanoCoulomb (nC) to ensure proximity close enough for effective nerve block[1,2] and above 20 nC to avoid inadvertent intraneural injection.[3]
Stimulating catheters can be inserted while stimulating at the tip of the catheter. The expected added value of stimulation during insertion is that by maintaining an appropriate motor response, optimal positioning of the tip in close proximity of the nerve can be ensured. However, this is based on the assumption that an appropriate motor response with a sufficiently low electrical charge equals adequate positioning of the catheter tip. In other words: A low electrical charge necessary to evoke an appropriate motor response signals close proximity of the catheter tip to the nerve, whereas an increase in the MEC signals an increase in the distance between catheter tip and the nerve. Establishing a correct position of the catheter tip not only increases the likelihood of adequate postoperative analgesia, it also allows the administration of the loading dose fractionated through the catheter, thus reducing the risk of systemic toxicity. An obvious disadvantage is that stimulating catheters are more expensive and more needle manipulation may be necessary.
Recent literature has focused on the sensitivity of an appropriate motor response evoked by nerve stimulation in determining needle or catheter-nerve contact using ultrasonography as a reference.[3-7] However, these studies have focused on the false-negative response; i.e. no appropriate motor response in case of needle-nerve contact as visualized by ultrasound. When an appropriate motor response can be elicited with a low electrical charge, close proximity to the nerve is evident. However, when the necessary electrical charge is relatively high, or an appropriate motor response is absent, there are three possibilities: the tip of the catheter may either still be close enough to the nerve to provide adequate analgesia, or it may be at an intermediate distance with partial analgesic effect, or it may be too far off and inadequate for postoperative analgesia. One clinical way to evaluate if the tip of the catheter is adequately placed, is measuring postoperative morphine consumption: With an appropriately placed catheter tip, morphine consumption is expected to be low, whereas consumption is expected to increase if the catheter tip is farther off from the nerves.
One could hypothesize that the relation between MEC and morphine consumption is proportional, i.e. there is a linear correlation between the necessary electrical charge at the tip of the stimulating catheter and the adequacy of the catheter, justifying the extra

manipulation to ensure close proximity to the nerve. The purpose of the present study is to investigate whether there is a correlation between the MEC at the tip of the blindly inserted stimulating catheter necessary to elicit an appropriate motor response, and the efficacy of the PNB catheter as determined by postoperative PCA morphine consumption. To investigate this hypothesis, we inserted a stimulating catheter as if it were a non-stimulating catheter and used the stimulation after placement as a measurement tool.

Materials and Methods

Ethics

Ethical approval for this study (Ethical Committee N° IRBN2009004) was provided by the Independent Review Board Nijmegen (Chairperson Dr. P. Koopmans) on 25 May 2009. This prospective blinded (for observer and patient) cohort study was registered at http://www.trialregister.nl (NTR2328) before onset of participant enrollment. Patients were informed about the study verbally and in writing and written informed consent was obtained from all patients. The study was conducted at the Sint Maartenskliniek Nijmegen, The Netherlands according to the Declaration of Helsinki and later revisions thereof and in accordance with the ICH guidelines for Good Clinical Practice.

Patients

Patients scheduled for cuff-, stability repair or acromioplasty of the shoulder under continuous brachial plexus block were assessed for eligibility during the preoperative screening visit. Eligible participants were all adults aged 18 or over with ASA physical health classification I-III. None of the patients were known with a history of alcohol/drug dependence or abuse or with hepatic or renal insufficiency. Exclusion criteria included contra-indications for regional anesthesia (infection at the injection site, coagulopathy), known hypersensitivity to amide-type local anesthetics or opioids, known history of peripheral neuropathy, use of chronic analgesic therapy, and inability to understand numerical pain scores or to operate a Patient-Controlled Analgesia (PCA) device.

Anesthetic procedure

Intravenous access and routine monitoring were established in all patients. Using ultrasound guidance (LOGIQ e 12L-RS probe, GE Healthcare, Wauwatosa, USA), a short axis view, and in-plane approach, in combination with nerve stimulation, a 5 cm insulated Tuohy needle (Arrow, Teleflex Medical BV, Hilversum, The Netherlands) was inserted in the interscalene area by an anesthesiologist experienced in ultrasound-guided interscalene block. After obtaining a correct needle position as determined by ultrasound and a motor response of deltoid, triceps or biceps muscle with a stimulus below 50 nC (0.1 ms, < 0.5 mA), a stimulating catheter (Arrow StimuCath, Teleflex Medical BV, Hilversum, The Netherlands) was inserted 2-5 cm past the needle tip without stimulation; i.e. as if it were a non-stimulating catheter. We defined the MEC as the minimal electrical charge with which a motor response of a muscle innervated by the brachial plexus could be elicited. After determination of the MEC, brachial plexus block was established by injecting a total volume of 20 mL ropivacaine 0.75% in fractionated doses through the catheter. Time was designated t = 0 upon conclusion of the loading dose. Sensory block of the shoulder was assessed using loss of sensation to pin prick 30 min after injection if possible without compromising operating room (OR) logistics. Sensory block was scored as absent, partial or complete. Surgery was performed under general anesthesia with propofol, remifentanil and a laryngeal mask airway.

Clinical assessments

After removal of the needle and fixation of the catheter and before administration of the loading dose, the MEC at the tip of the catheter necessary to evoke a motor response was determined and registered. If no response was present on the maximum current intensity of 1 mA at 0.1 ms, the pulse width was increased to 0.3 ms and then to 1.0 ms, the electrical charge thus varying from 0 to 1000 nC (nC = mA × ms ×1000); if no response was obtained at 1000 nC, the current scale was increased to 5 mA and a motor response was sought up to a maximum electrical charge of 5000 nC. The observer of motor response (KS) was blinded for the electrical charge.

One hour after administration of the brachial plexus loading dose, a continuous infusion of ropivacaine 0.2% 8 mL.h^{-1} was connected to the brachial plexus catheter and maintained until t = 24 h. Upon arrival in the recovery, the pain score (numerical rating scale: NRS 0-10) was noted and a PCA morphine device set up to deliver incremental doses of 1 mg of morphine with a lockout time of 5 minutes and no background infusion was connected to the intravenous cannula. Patients were instructed in the use of the PCA device preoperatively to maintain postoperative pain scores (NRS) at or below 3.

At t = 24h, the continuous infusion through the catheter was stopped and the PCA device was disconnected by the investigator (KS). The total amount of administered morphine was registered. Patients were asked for their NRS at time of disconnection and their average and maximal NRS during the studied 24 h.

Primary outcome measures include the MEC necessary to evoke an appropriate motor response at the tip of the blindly inserted stimulating catheter and PCA morphine consumption during the first 24 h.

Sample size and statistical analysis

In the absence of relevant data considering variation in electrical charge, we assumed ρ = 0.5 the smallest correlation to be relevant. The sample size needed for this correlation with α = 0.05 and a power of 0.9, was calculated to be 34 patients. To compensate for drop-out, we chose to include 40 patients in our study.

Data were analyzed using the GraphPad Prism 6 software (GraphPad Software Inc, San Diego, CA). Data are presented as mean (SD) [range] or proportions. Statistical analysis used the Spearman's Rho for correlation coefficient calculation.

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Results

Forty patients were included. One patient showed symptoms of systemic toxicity (tinnitus, metallic taste) after 14 mL of ropivacaine 0.75% through the interscalene catheter. Injection was discontinued and the catheter was removed. The patient was treated with oxygen and prophylactic intravenous administration of lipid emulsion. No further treatment was necessary, symptoms resolving completely within a few minutes. Measured MEC at the tip of the catheter in this patient was 1425 nC.
The protocol was violated in another 5 patients. One patient mistakenly received a loading dose of 30 mL instead of 20 mL. In one patient the catheter was removed postoperatively because the patient was uncomfortable with it; later, this patient received an additional single shot interscalene block with 20 mL ropivacaine 0.2% because of pain; MEC in this patient was 72 nC. Three patients received an additional bolus of ropivacaine through the interscalene catheter immediately upon arrival at the recovery because of high pain scores. MEC values in these patients were 46, 68 and 120 nC respectively. These three patients had a complete sensory block of the shoulder prior to surgery. The six patients with protocol violations (Table 1) were excluded from subsequent analysis.

Table 1. Protocol Violations

Event	MEC* (nC)
Toxic reaction after 14 mL loading dose ropivacaine 0.75%	1425
Loading dose of 30 instead of 20 mL ropivacaine 0.75%	46
Catheter discomfort and postoperative pain (catheter removed, single shot interscalene block with ropivacaine 0.2%)	72
Postop pain requiring extra ropivacaine (20 mL ropi 0.2%)	46
Postop pain requiring extra ropivacaine (10 mL ropi 0.75%)	68
Postop pain requiring extra ropivacaine (20 mL ropi 0.2%)	120

*MEC = Minimal electrical charge necessary to elicit an appropriate motor response.

Patient and surgical characteristics of the 34 patients in study are shown in Table 2.
All patients showed an appropriate motor response (deltoid, biceps or triceps muscle) during catheter stimulation, except for 2; one patient showed a phrenic nerve response and one patient had a response of the median nerve (finger flexion).

Table 2. Patient and Surgical Characteristics

	Total (n = 34)
Sex; M/F	20/14
Age; years	49 (14)
BMI; kg.m-2	27 (4)
Duration of surgery; min	47 (16)
Type of surgery	Open rotator cuff repair (n = 12) Capsular shift (n = 11) Scopic acromioplasty (n = 4) Scopic rotator cuff repair (n = 2) Latissimus dorsi transfer (n = 2) Open acromioplasty (n = 1) Open Bankart repair (n = 1) Latarjet slap repair (n = 1)

Values are numbers or mean (SD)

Sensory block of the shoulder at 30 min after injection could be assessed in 19 patients. In the remaining 15 patients surgery had already started before this time point. There were no postoperative complications related to the anesthetic procedure.
In three patients a different PCA device was mistakenly connected, with a continuous infusion of morphine 0.5 mg.h^{-1}. Because these patients still required extra morphine boluses, they were not excluded from analysis. Total administered amount of morphine in these patients was 10, 23 and 27.7 mg; MEC values were 246, 38 and 60 nC respectively.
Mean morphine consumption was 8.9 (9.9) [0-29] mg (95% CI of the mean 5.4 to 12.3, n = 34). Data on individual parameters and clinical outcome measures are summarized in Tables 3 and 4 respectively. Spearman's Rank Correlation Coefficient between the electrical charge (nC) at the tip of the catheter and morphine consumption was rs= -0.26 (95% CI -0.56 to 0.09, n = 34). Figure 1 shows a scatterplot of morphine consumption as a function of the electrical charge at the tip of the catheter in individual patients.

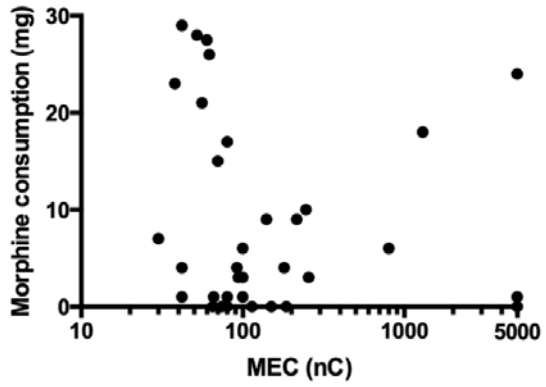

Fig. 1.
Scatterplot of morphine consumption related to the electrical charge at the tip of the catheter in individual patients. Note that the X-axis is not linear.

Table 3. Individual Outcome Parameters

M/F	Response*	Sensory block at 30 min	NRS Recovery**	24 h Morphine consumption; mg	MEC††; nC
F	MD†	complete	0	7	30
F	MD	complete	0	23	38
M	MD	unable¶ǁ	6	29	42
F	MB‡	unable	2	4	42
M	MT§	complete	0	1	42
M	MB	complete	0	28	52
M	MT	complete	4	21	56
F	MT	complete	4	28	60
F	MD	unable	0	26	62
M	MD	partial	0	0	65
F	MT	complete	0	1	66
F	MB	unable	4	15	70
M	MB	unable	0	0	74
M	MB	unable	0	1	80
M	MT	unable	0	17	80
M	MB	unable	0	0	80
M	MT	complete	0	4	92
F	MT	complete	0	3	94
M	MD	unable	0	1	100
M	MT	unable	0	3	100
F	MT	partial	0	6	100
M	MT	complete	0	0	114
M	MB	unable	0	9	140
M	MD	complete	0	0	150
F	MB	complete	0	4	180
M	MT	complete	0	0	186
M	MT	unable	0	9	216
F	Median nerve	complete	5	10	246
F	MB	unable	0	3	255
F	MD	complete	0	6	800
F	MT	unable	0	18	1300
M	MT	partial	0	1	5000
M	MB	unable	0	0	5000
M	Phrenic nerve	partial	0	24	5000

*Response = motor response to nerve stimulation. †MD = Deltoid muscle; ‡MB = Biceps muscle; §MT = Triceps muscle. ¶ǁUnable = Sensory block assessment at 30 min. not possible because patient already in surgery. **NRS recovery = numerical rating scale for pain upon arrival in the recovery room; ††MEC = Minimal electrical charge necessary to evoke an appropriate motor response.

Table 4. Clinical Outcome Measures

	Total (n = 34)
MEC (nC)	589 (1414) [30 – 5000]
NRS* recovery	0.7 (1.7) [0 – 6]
NRS t = 24h	2.1 (2.1) [0 – 7]
NRS average during 24h	2.5 (2.0) [0 – 7]
NRS max during 24 h	3.9 (2.8) [0 – 9]
Morphine consumption; mg	8.9 (9.9) [0 – 29]

Values are mean (SD) [range]. *NRS = numeric rating scale for pain.

Discussion

The purpose of our study was to investigate the hypothesis that the relation between MEC and morphine consumption is proportional. We found no correlation between the minimal electrical charge at the tip of the stimulating catheter necessary to evoke an appropiate motor response and the efficacy of the PNB catheter for brachial plexus block.

The theoretical advantage of a stimulating catheter is that if stimulation of the catheter tip with a low charge elicits an appropriate motor response, correct catheter position at the time of stimulation may be assumed, although catheter tip migration at a later stage may of course still occur. One of the problems associated with continuous PNB is postoperative pain as a result of malfunctioning of the PNB catheter. The tip of the PNB catheter being too far away from the target nerves to establish effective pain relief may already occur during catheter insertion, or it may be caused by catheter tip migration during or after surgery. In our study the loading dose was administered through the catheter prior to surgery and the observation that four patients with a MEC less than 100 nC had pain scores at or above 4 upon arrival in the recovery room indicates that the interscalene block in these patients was insufficient despite a low MEC.

Stimulating catheters are more expensive than non-stimulating catheters, but the literature is mixed regarding the beneficial effects of the former. Some authors report advantages such as a shorter onset time, better postoperative analgesia or reduced postoperative local anesthetic and/or morphine consumption.[8,9] A semiquantitative systematic review found evidence for better postoperative analgesia with stimulating catheters.[10] Others fail to identify benefits of stimulating catheters and report no differences compared with traditional non-stimulating catheters.[11,12] Stevens et al. reported no differences in postoperative pain when comparing stimulating versus non-stimulating catheters for continuous interscalene block, but better functional outcome six weeks after surgery.[13]

There is debate about the negative predictive value of nerve stimulation and the proximity of the needle tip to the nerve. Perlas et al. noticed that occasionally a motor response to nerve stimulation up to 1.5 mA (150 nC) may be absent despite needle-nerve contact as observed by ultrasound.[14] In a study comparing the sensitivity of paresthesia and a motor response to nerve stimulation with an electrical charge of 50 nC or less, the sensitivity to nerve stimulation was 74.5% to detect needle-nerve contact as observed by ultrasound.[6] Using stimulating catheters and ultrasound as a reference, Altermatt et al. found that the sensitivity of an electrical charge of 50 nC to identify catheter-nerve contact was 64%.[4] Tsai et al. reported that with intraneural needle placement as determined by ultrasound, a

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motor response could be evoked with an average stimulus of 0.56 mA (56 nC), but in 12.5% of the cases the MEC ranged from 80-180 nC.[3] In a study quantifying the motor response with ultrasound-guided interscalene block, Sinha et al. found no differences in block characteristics between the stimulus eliciting a motor response being above or below 0.5 mA (50 nC).[15] The absence of correlation between the MEC and postoperative morphine consumption found in this study indicates that the MEC has no predictive value about the postoperative efficacy of the PNB catheter.

The rationale for the extra cost of a stimulating catheter is in its positive predictive value, i.e. the association between an appropriate motor response following a MEC at or below a predefined level, and the incidence of a properly positioned PNB catheter as determined f.e. by postoperative PCA morphine consumption. The results of our study show that the positive predictive value of a lower MEC is not associated with a reduction in morphine consumption, indicating that the possibility of catheter tip stimulation does not result in a clinically relevant advantage. This indicates that the extra cost of a stimulating catheter is not balanced by a better efficacy of the catheter.

Our study has several limitations. Due to OR logistics, sensory block could not be assessed at 30 min in 15 patients because surgery had already started at that time. However, since the primary outcome parameter was the efficacy of the PNB catheter as determined by 24 h morphine consumption, verifying sensory block at 30 min was not strictly necessary. In addition, 12 of these 15 patients had an adequate sensory block upon arrival at the recovery, as judged by a NRS of 0.

PCA morphine consumption as a measure of PNB catheter efficacy may be criticised as it is an indirect tool at best; morphine consumption reflects the intensity of postoperative pain, but patients may use the PCA device for other discomforts as well. However, it is less time-consuming and less bothersome for patients than pin-prick assessments of sensory block at regular intervals, and in general the relation between morphine consumption and postoperative pain will be proportional.

It may be argued that we did not investigate PNB catheter efficacy per se because the effect of the loading dose alone will last 8-12 h, but may last as long as 20 h and we measured morphine consumption only up to 24 h. However, since the loading dose was administered through the PNB catheter after positioning the catheter and determining the MEC, we believe that our findings adequately reflect the relation between MEC and catheter efficacy.

In conclusion, our results show that in interscalene brachial plexus block the MEC at the catheter tip necessary to evoke an appropriate motor response has no correlation with catheter efficacy as determined by postoperative 24 h morphine consumption.

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Chapter 07

General discussion, future perspectives and conclusions

General discussion, future perspectives and conclusions

The main purpose of this thesis was to investigate different factors determining the duration of peripheral nerve blockade. In this chapter our main findings are summarized and discussed in relation to the current literature, potential limitations and clinical implications of the studies performed are described and recommendations for future research are given. Finally, the conclusions of this thesis are presented.

Discussion of main findings

The most important prerequisites for the use of peripheral regional anesthesia in daily clinical practice are success rate and safety. From a safety perspective a lower dose is preferable and using ultrasound guidance, adequate peripheral nerve block can be established with a lower volume. However, the effect of dose reduction on block duration was previously unknown. Recent literature has focused on the relation between volume, concentration and dose of local anesthetic and pharmacodynamic parameters such as duration of sensory and motor block. Some studies found a positive correlation between volume of local anesthetic and duration of postoperative analgesia. In these studies, the higher volume was associated with a higher dose as well.[1,2] Serradell et al.[3] compared the number of complete sensory blocks for different volumes (20, 28, 36 mL) of mepivacaine 1% in axillary block and found no differences in success rate, onset time and duration of analgesia among the 3 groups. The results suggest that 200 mg mepivacaine in a volume of 20 mL also provides adequate axillary block and that increasing the volume/dose of mepivacaine tot 280 or 360 mg does not result in a higher success rate or al longer duration of analgesia. In a dose-ranging study of 0.5% bupivacaine and ropivacaine for sciatic nerve block, Nader et al.,[4] found that injection volumes greater than or equal to 10 mL produced complete sensory and motor block within 30 minutes. Volumes greater than 10 mL did not extend the duration of the sensory or motor block. Injection volumes of 2.5 and 5 mL were associated with delayed onset and decreased block duration and a greater fraction of subjects experiencing pain behind the knee.

In **Chapter 2**, a local anesthetic dose reduction of 62.5% resulted in an approximate 17% shorter overall sensory and 19% motor block duration, and a reduction in time to first request for postoperative analgesia (TTFR) of approximately 30%. The difference in block duration observed in Chapter 2 was the effect of either a reduction in volume from 40 to 15 mL mepivacaine 1.5%, a reduction in dose from 600 to 225 mg mepivacaine, or a combination of both.

In **Chapter 3** we describe the results of a follow up study on the effect of local anesthetic concentration, dose and volume on the duration of single shot ultrasound-guided axillary brachial plexus block with mepivacaine. We compared the effects of different doses in equal volumes (30 mL mepivacaine 1% and 30 mL mepivacaine 1.5%) as well as equal doses in different volumes (20 mL mepivacaine 1.5% and 30 mL mepivacaine 1%) for axillary brachial plexus block. Our results show that the higher dose (and concentration) administered in Group 30 mL mepi 1.5% resulted in a longer duration of sensory and motor block as compared to Group 30 mL mepi 1%. A remarkable finding of our study was a tendency for a longer duration for sensory and motor block in Group 20 mL mepi 1.5% as compared to Group 30 mL mepi 1%, both for overall duration (approximately 13% and 15%) as well as for the individual nerves (values ranging from 9-16% and 10-22% for duration of sensory and motor block

respectively). This may indicate that when using equal doses, a higher concentration/lower volume results in longer duration. In a study using multivariate Cox regression to assess the effect of different volumes and concentrations of ropivacaine on the duration of analgesia following interscalene block for shoulder surgery, Fredrickson et al.[5] concluded that both volume and concentration affect duration independently. More recently, Cappelleri et al.[6] compared duration of sensory block with 12 mL mepivacaine 2% (240 mg) versus 24 mL mepivacaine 1% (240 mg) for double injection sciatic nerve block and found no indication for altered onset time and block duration. These latter data suggest that total dose of local anesthetic is the main determinant of peripheral nerve block duration.

In **Chapter 3**, reducing the volume/dose from 30 mL mepivacaine 1.5% (450 mg) to 20 mL mepivacaine 1.5% (300 mg) did not result in a shorter duration of sensory or motor block. Combining the observations from Chapter 2 and 3, it seems clear that the relation between a reduction in dose and the duration of nervous blockade is not proportional. Reducing the dose of mepivacaine 1.5% from 600 mg (40 mL) to 300 mg (20 mL) results in a modest change in the median duration of nervous blockade of approximately 5%; a further decrease to 225 mg (15 mL) or a decrease in concentration to 1% (300 mg, 30 mL) results in a decrease in duration of approximately 18% and 15% respectively. It seems therefore that in axillary brachial plexus block, the optimal balance between dose reduction without significantly affecting duration of nervous blockade lies around 20 mL mepivacaine 1.5%.

From the above-described findings we conclude that for a particular block, a minimum amount of a specific local anesthetic is necessary for an adequate nerve block and increasing dose or volume will not extend the duration of sensory or motor block. In a recent review, Eng et al also concluded that there appears to be a dose threshold beyond which improvements in onset time, block intensity and analgesic duration become less significant.[7]

Despite the aim for dose reduction to enhance safety, in case of lower limb surgery a combination of blocks and consequently higher doses of local anesthetics is often necessary. **Chapter 4** was the first study describing the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine for combined sciatic/femoral nerve block. Patients received 60 mL ropivacaine either without (Group R) or with epinephrine 5 µg/ml (Group RE). Obviously the major concern when using high doses of local anesthetic is systemic toxicity. Ropivacaine has a high degree of protein binding in plasma (94%)[8], mainly to α-1 acid glycoprotein. As only unbound ropivacaine is capable of passing membranes, the free ropivacaine concentration in serum is the determinant of local anesthetic-related central nervous system and cardiac toxicity. Knudsen et al.[9] previously defined the toxic threshold for free ropivacaine in arterial samples as 0.56 [0.34-0.85] µg/mL. The average maximum free ropivacaine serum concentration in our study was 0.16 ± 0.08 [0.07-0.30] µg/mL in group R and 0.12 ± 0.04 [0.09-0.17] µg/mL in group RE. Total and free serum concentrations of ropivacaine remained well below the assumed threshold for local anesthetic systemic toxicity. The addition of epinephrine prolonged t_{max} significantly, but the difference in C_{max} was statistically not significant. Several other studies found a decrease in C_{max} and an increase in tmax as a result of adding epinephrine to ropivacaine for epidural[10,11], caudal[12], or regional (thoracic paravertebral block)[13] anesthesia.

Although the number of subjects in our study does not allow conclusions on the issue of safety, in the past 10 years, more than 5,000 patients at our institution have received a combined sciatic/femoral nerve block with 450 mg of ropivacaine. During this period, we have observed only one patient with mild signs of delayed systemic toxicity (anxiety and restlessness, 45 min after injection) that resolved within minutes without treatment. The results of Chapter 4 support our clinical experience that a combined sciatic/femoral nerve block with 450 mg ropivacaine in adult patients > 70 kg and < 60 years is safe.

To prevent the need for larger doses of local anesthetic, in recent literature several adjuncts have been tested with single-shot peripheral nerve block in order to prolong duration of analgesia. F.e. perineural dexamethasone (4 or 8 mg) prolongs the duration of analgesia after local anesthetic peripheral nerve block and reduces cumulative morphine consumption and PONV without serious side effects.[14] However, postoperative infection rate may increase and further studies are needed to define the best route of administration (iv vs. perineural) and optimal balance between dose, effects and side effects. Moreover, none of the adjuncts have been approved for perineural use, therefore caution is recommended concerning side effects and potential neurotoxicity. Nonetheless, Kirksey et al.[15] recently concluded in a systemic qualitative review that buprenorphine, clonidine, dexamethasone, magnesium and dexmedetomidine are promising agents for use in prolongation of local anesthetic peripheral nerve blocks.

In Chapter 4 we found a median time to first request of analgesia (TTFR) of 17 [12.5-22] h in Group RE and 3.5 [3-17] h in the Group R, suggesting a prolonged duration of action when adding epinephrine. The difference in TTFR between the groups in Chapter 4 was statistically not significant and because our study was not powered to make comparisons, these data have not been published. Therefore we designed the study in Chapter 5 to investigate if the addition of epinephrine would result in significant lengthening of the TTFR.

In **Chapter 5** we were unable to confirm this expected difference in the duration of postoperative analgesia by adding epinephrine 5 µg/ml to 30 mL ropivacaine 0.75% for popliteal nerve block. The difference in the median TTFR between the groups was large (367 min), but the data were not normally distributed and showed a large variation. Therefore, the Hodges Lehman estimate of the median difference between groups is a better utility. This was 71 min (95% CI -415 – 473). The absence of a significant difference may be explained on the basis of the intrinsic vasoconstrictive properties of ropivacaine. However, it may also be caused by a Type II error due to a large interindividual variation in TTFR. Similarly, Weber et al.[16] found no difference in time to first request for postoperative analgesia between ropivacaine 0.5% with and without epinephrine for femoral nerve block.

In contrast, other studies have found a significantly longer duration of postoperative analgesia when adding epinephrine to short or intermediate acting local anesthetics. Kämmerer et al.[17] described significantly longer patient reported duration of soft tissue anesthesia when using articaine 4% with vs. without epinephrine 1:100,000 for inferior alveolar block. Comparably, Dogru et al.[18] found a significantly longer time to first sensation of pain after axillary brachial plexus block with 35 mL lidocaine 1.5% with either 25 or 200 µg of epinephrine as compared to lidocaine alone. Furthermore, Song at al.[19] found significantly extended duration of sensory and motor block and time to first pain sensation when adding

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epinephrine 1:200,000 to 40 mL mepivacaine 1% as compared to mepivacaine alone for infraclavicular brachial plexus block.

Epinephrine is believed to prolong duration of analgesia because it slows absorption of local anesthetics at the site of injection due to vasoconstriction. This suggests that epinephrine does not prolong duration of postoperative analgesia when added to ropivacaine, due to intrinsic vasoconstrictive properties of the latter.

As described in Chapter 1, another method of providing prolonged duration of analgesia is by inserting a perineural catheter for continuous infusion of low dose local anesthetic. The analgesic efficacy of continuous postoperative peripheral nerve block depends on correct placement of the perineural catheter, i.e. in proximity to the nerve. Stimulating catheters offer the possibility of nerve stimulation via the tip of the catheter. This may be advantageous, because placement of the catheter tip close to the nerve can be verified by a correct motor response following electrical stimulation. However, stimulating catheters are more expensive.

Cappelleri et al, following the study of Paqueron et al.[20], recently demonstrated that use of a stimulating catheter halved the EV50 (minimum effective anesthetic volume in 50% of patients) of mepivacaine 1.5% required for lumbar plexus block when the local anesthetic was injected through the catheter, compared with a conventional non-stimulating catheter.[21]

The results in **Chapter 6** show that in interscalene brachial plexus block the minimal electrical charge (MEC) at the catheter tip necessary to evoke an appropriate motor response has no correlation with catheter efficacy as determined by postoperative 24h morphine consumption after cuff-, stability repair or acromioplasty of the shoulder. Mean morphine consumption was 8.9 (±9.9) [0-29] mg (95% CI of the mean 5.4 to 12.3 mg, n = 34) in the 24h study period. This indicates adequate pain relief with the use of a continuous brachial plexus block after shoulder surgery. The absence of correlation between the MEC and postoperative morphine consumption found in Chapter 6 indicates that the MEC has no predictive value about the postoperative efficacy of the peripheral nerve block catheter. This means that the extra cost of a stimulating catheter as compared to a non-stimulating catheter is not balanced by a better performance.

When using ultrasound guidance, nerve stimulation may no longer be a prerequisite for optimal placement. Recent literature has focused on the added value of using a stimulating catheter in combination with ultrasound guidance. Brooks et al.[22] found no differences with regard to catheter visibility, block onset or success rate of ultrasound-guided continuous sciatic nerve block with either stimulating needle and catheter or echogenic needle and catheter. However, the stimulating group required more needle redirections, had a longer procedure time and greater patient discomfort. Farag et al.[23] compared ultrasound guidance alone with either ultrasound guidance plus needle stimulation or ultrasound guidance plus catheter stimulation for insertion of femoral nerve catheters for total knee arthroplasty and found no superiority of one method over another in pain scores or opioid requirement. Block performance time was shorter and costs were lower for the ultrasound-alone group.

Besides, from a safety perspective, there is an expanding body of literature describing stimulating catheter entrapment.[24] Taking all this into consideration, we come to the conclusion that when using ultrasound guidance, there is no added value for stimulating catheters in current practice. Many aspects of continuous peripheral nerve block need further research including optimal catheter insertion techniques, infusate(s) and adjuvants, details of optimizing ambulatory infusions, and prevention of rare adverse effects.[25]

Potential limitations

There are several limitations in the design of the studies described in this thesis.
When investigating duration of peripheral nerve block, sensory and motor block testing at regular time intervals (as done in Chapter 2 and 3) is the most objective method. TTFR, as used in Chapter 4 and 5, is a subjective measure of duration of analgesia. However, when using long acting local anesthetics like ropivacaine, offset testing would take 24 – 48 h, including nighttime measurements, which is bothersome for patients. Furthermore, from a clinical perspective, duration of analgesia may be more important than duration of sensory block. In Chapter 6, we use morphine consumption as a measure of catheter efficacy, which also is an indirect tool at best. However, in general, the relation between morphine consumption and postoperative pain will be proportional and we therefore believe that this method was valid.

A second limitation is the probability of lack of power in Chapters 3 and 5. For both studies, a power analysis was performed based on data found in the existing literature and we compensated for possible larger variations in standard deviation. In Chapter 3, our power analysis was based on a clinically relevant difference of 60 min, whereas in retrospect and from a scientific perspective smaller differences may also be interesting. As a result of the large variation in our data in Chapter 5, the risk of a Type II error is considerable. Possibly larger sample sizes would have unveiled significant differences. This also accounts for the difference in C_{max} and TTFR as described in Chapter 4, although this was a pilot study, not powered to make comparisons.

And last, with the advances in ultrasound, there has been a rapid refinement in block placement techniques. In Chapters 2, 3 and 4, relatively high concentrations of mepivacaine (450 and 600 mg) and ropivacaine (450 mg) are being used. The use of ultrasound allows for a reduction in local anesthetic dose without compromising block characteristics. However, exceeding the maximum recommended dose of ropivacaine and mepivacaine still occurs regularly. As such there remains a need for pharmacokinetic and -dynamic data on doses that are higher than the maximum recommended dose. Authoritative statements about safety obviously require larger numbers.

Clinical implications

The results of the studies described in this thesis may have various implications for clinical practice. With regard to the effect of dose reduction on peripheral nerve block duration, our results suggest that when using equal doses, a higher concentration/lower volume results in a longer duration, but total dose seems to be the main determinant of peripheral nerve block duration. However, our findings also suggest that there is a threshold dose of local anesthetic: increasing the dose above this threshold will not result in a further increase in the duration of sensory or motor block.
In case of multiple nerve blocks, the usage of higher than recommended doses (up to 450 mg ropivacaine or 600 mg mepivacaine for patients > 70 kg and < 60 years of age) seems to be safe. Epinephrine may be added to ropivacaine in order to enhance safety, but it has no beneficial effect on block duration. Lastly, our results indicate that, when using a stimulating catheter, the MEC has no predictive value on the postoperative efficacy of the peripheral nerve block catheter.

Future Perspectives

Current clinical practice in (orthopedic) surgery is shifting towards the patient not being 'ill', but rather being seen as a healthy person in need of some 'repairment'. This 'fast-track surgery' or 'fast-track rehabilitation', consists of several elements such as preoperative education, minimally invasive surgery, optimal pain relief, and early mobilization. The goal of modern anesthetic techniques is to facilitate a short recovery time and to minimize postoperative nausea and vomiting and pain. Optimal control over postoperative pain is a determining factor for the success of fast-track rehabilitation and ambulatory care and regional anesthetic techniques in combination with a multimodal pain regimen play a vital role. Trend analyses show that peripheral nerve blocks are increasingly being used in both inpatient and ambulatory orthopedic surgery.26 However, adequate pain relief by means of peripheral nerve block may hamper the goals of early mobilization and early discharge.

Future research should focus on finding the optimal balance between adequate analgesia and minimal interference with the prerequisites of fast-track rehabilitation. Several issues come into view, like fine-tuning of multimodal analgesic regimens in combination with a peripheral nerve block. Secondly, the optimal drug and dose for individual blocks should be defined: further research is necessary to determine whether a threshold dose exists above which pharmacodynamic parameters do not further improve significantly.

From a safety perspective, future research should focus on prolonging duration of analgesia without the need for larger doses of local anesthetics. This may be accomplished by investigating non-neurotoxic additives to local anesthetics that provide a more differential block, i.e. prolonging the duration of sensory block without affecting the duration of motor block. Furthermore, strategies for safe mobilization in the presence of a partial motor block should be developed as well as protocols for safe discharge of patients with a functional peripheral nerve catheter. To prevent the need for a perineural catheter, further research could focus on local infiltration of multivesicular liposomes containing bupivacaine, which may have promising implications for prolonged postoperative analgesia.

Last but not least, there are clear indications that severe postoperative pain predisposes to the development of chronic pain, which has major social and economical implications. Since peripheral nerve block is capable of providing optimal postoperative pain relief, this may be associated with a reduction of the incidence or severity of chronic pain following surgery. Long-term outcome studies are necessary to substantiate this.

Conclusions

The main conclusions that can be drawn from the results of the studies presented in this thesis are:

- In axillary brachial plexus block with mepivacaine 1.5%, volume reduction from 40 mL to 15 mL (62.5%) shortens the overall duration of sensory and motor block by approximately 17-19% and reduces sensory and motor block duration of individual nerves with 18-40%. (Chapter 2)
- In axillary brachial plexus block with mepivacaine 1.5%, volume reduction from 40 to 15 mL (62.5%) decreases the time to first request for postoperative analgesia by approximately 30%. (Chapter 2)
- A higher dose (and concentration) of mepivacaine results in a longer duration of sensory and motor axillary brachial plexus block. (Chapter 3)
- It seems that in axillary brachial plexus block, the optimal balance between dose reduction without significantly affecting duration of nervous blockade is 20 mL mepivacaine 1.5%. (Chapter 3)
- Total and free serum concentrations of ropivacaine after a combined sciatic/femoral nerve block with 450 mg ropivacaine with or without epinephrine 1:200,000 remain well below the assumed threshold for local anesthetic systemic toxicity. (Chapter 4)
- The addition of epinephrine to ropivacaine 0.75% for popliteal nerve block does not result in an extension of the duration of postoperative analgesia. (Chapter 5)
- In interscalene brachial plexus block the minimal electrical charge at the tip of a stimulating catheter necessary to evoke an appropriate motor response has no correlation with catheter efficacy as determined by postoperative 24h morphine consumption. (Chapter 6)

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07

Summary

Summary

Peripheral nerve block (PNB) is popular among anesthesiologists and patients for peri- and postoperative pain relief. **Chapter 1** describes the relevant anatomy, techniques and local anesthetics used for peripheral nerve blocks. Duration of peripheral nerve block depends on several factors such as the choice of local anesthetic (LA), the presence of adjuncts such as epinephrine, and the use of a catheter for prolonged infusion. Choices can be made dependent on the purpose of the nerve block; is it for intraoperative anesthesia and/or should it provide (prolonged) postoperative analgesia.

Intraoperative anesthesia for minimally painful surgery: short acting local anesthetics

The most important prerequisites for the use of peripheral regional anesthesia in daily clinical practice are success rate and safety. From a safety perspective a lower dose is preferable and using ultrasound guidance, adequate peripheral nerve block can be established with a lower volume. However, the effect of dose reduction on block duration was previously unknown.

In **Chapter 2**, we compared the duration of sensory and motor axillary brachial plexus block with 15 or 40 mL mepivacaine 1.5%. A local anesthetic volume reduction of 62.5% resulted in an approximate 17% shorter overall sensory and 19% motor block duration, and a reduction in time to first request for postoperative analgesia (TTFR) of approximately 30%.

In **Chapter 3** we describe the results of a follow up study on the effect of local anesthetic concentration, dose and volume on the duration of single shot ultrasound-guided axillary brachial plexus block with mepivacaine. Our results show that the higher dose (and concentration) administered in Group 30 mL mepi 1.5% resulted in a longer duration of sensory and motor block as compared to Group 30 mL mepi 1%. We found no difference in duration between 20 or 30 mL mepi 1.5%. A notable finding of our study is a tendency for a longer duration for sensory and motor block in Group 20 mL mepi 1.5% as compared to Group 30 mL mepi 1%.

Intraoperative anesthesia and postoperative analgesia: long acting local anesthetics with additives

For surgery where some postoperative pain is expected, a longer acting local anesthetic can be used. This can provide surgical anesthesia and cover the first postoperative hours in terms of postoperative analgesia. In case of lower limb surgery a combination of blocks and consequently higher doses of local anesthetics is often necessary.

Chapter 4 was the first study describing the pharmacokinetic profile in serum of 450 mg ropivacaine with and without epinephrine for combined sciatic/femoral nerve block. Patients received 60 mL ropivacaine 0.75% either without (Group R) or with epinephrine 5 µg/ml (Group RE) and venous blood samples were obtained during 48h following block placement. Total and free serum concentrations of ropivacaine remained well below the assumed threshold for local anesthetic systemic toxicity. The addition of epinephrine prolonged t_{max} significantly, but the difference in C_{max} was statistically not significant. With regard to duration of analgesia, we found a large non-significant difference in median time to first request of analgesia (TTFR). As our study was not powered to make comparisons, we designed the study in Chapter 5 to investigate if the addition of epinephrine results in significant lengthening of the TTFR.

In **Chapter 5** we were unable to confirm this expected difference in the duration of postoperative analgesia. Thirty-eight patients were included to receive ultrasound guided continuous popliteal nerve block with ropivacaine 0.75% either without (ROPI) or with epinephrine 5 µg/mL (ROPI-EPI). We compared duration of postoperative analgesia as reflected by the time to first request for postoperative analgesia (TTFR) through the popliteal nerve catheter. The absence of a significant difference may be explained on the basis of the intrinsic vasoconstrictive properties of ropivacaine. However, it may also be caused by a type II error due to a large variation in the individual TTFR.

Postoperative prolonged action with a perineural catheter

If postoperative pain is expected to be severe and longer lasting, e.g. in arthroplasty, a nerve catheter can be inserted for prolonged infusion of local anesthetic. For continuous nerve block, stimulating and non-stimulating catheters can be used.
Chapter 6 was designed to investigate whether there is a correlation between the minimal electrical charge (MEC) at the tip of the stimulating catheter, and the efficacy of the interscalene brachial plexus catheter as determined by 24h postoperative morphine consumption. The absence of a correlation between the MEC and postoperative morphine consumption found in Chapter 6 indicates that the MEC has no predictive value about the postoperative efficacy of the PNB catheter. This means that the extra cost of a stimulating catheter as compared to a non-stimulating catheter is not balanced by a better performance.

Chapter 7 of this thesis summarizes and discusses our main findings in relation to the current literature and gives recommendations for future research.

Samenvatting

Samenvatting

Perifere zenuwblokkades kunnen voor zeer goede pijnstilling zorgen tijdens en na operaties en zijn daarom populair bij patiënten en anesthesiologen. In **hoofdstuk 1** worden de relevante anatomie, de technieken en de lokaal anesthetica beschreven die nodig zijn voor perifere zenuwblokkades (PZBs). De werkingsduur van zo'n blokkade is afhankelijk van verschillende factoren, zoals keuze van lokaal anestheticum (LA), het toevoegen van een additief zoals adrenaline en het gebruik van een zenuw katheter voor langdurige infusie. De keuzes worden gemaakt afhankelijk van het doel van de zenuwblokkade: moet het een pijnvrije operatie mogelijk maken en/of moet het postoperatief langdurig pijnstilling geven.

Intraoperatieve anesthesie voor chirurgie zonder veel pijn nadien: kort werkende lokaal anesthetica

De belangrijkste voorwaarden voor het gebruik van regionale anesthesie in de dagelijkse klinische praktijk is het succespercentage en de veiligheid. Vanuit veiligheidsoogpunt heeft een lagere dosis lokaal anestheticum de voorkeur. Met het gebruik van echogeleiding kan een adequaat blok verkregen worden met een kleiner volume LA. Desondanks was het effect van een dosisverlaging op de werkingsduur onbekend.
In **hoofdstuk 2** hebben we de werkingsduur vergeleken van sensibel en motorisch axillair blok met 15 of 40 ml mepivacaïne 1.5%. Een volumereductie van 62.5% resulteerde in ongeveer 17% kortere sensibele en 19% kortere motorische blokkade. De tijd tot eerste vraag naar postoperatieve pijnstilling (TTFR) was ongeveer 30% korter.
In **hoofdstuk 3** beschrijven we de resultaten van een vervolgstudie naar het effect van concentratie, dosis en volume van het lokaal anestheticum op de werkingsduur van echogeleid axillair brachiaal plexusblok met mepivacaïne. Wij vonden daarbij dat de hogere dosis (en concentratie) toegediend in groep 30 ml mepi 1.5% resulteerde in een langere werkingsduur van sensibele en motorische blokkade in vergelijking met groep 30 ml mepi 1%. We hebben geen verschil in werkingsduur gevonden tussen 20 of 30 ml mepivacaïne 1.5%. Opvallend was dat we een neiging tot langere sensibele en motorische blokkade hebben gevonden in groep 20 ml mepi 1.5% in vergelijking met 30 ml mepi 1%.

Intraoperatieve anesthesie en postoperatieve analgesie: lang werkende lokaal anesthetica met additieven

Voor operaties waar (beperkte) postoperatieve pijn voorzien is, kan een lang werkend lokaal anestheticum gebruikt worden. Dit zorgt voor gevoelloosheid tijdens de operatie en dekt de pijnstilling gedurende de eerste uren na de operatie. Voor onderbeenoperaties is vaak een combinatie van verschillende zenuwblokkades nodig waarbij hogere doseringen lokaal anestheticum gebruikt worden.
Hoofdstuk 4 beschrijft als eerste studie het farmacokinetisch profiel in serum van 450 mg ropivacaïne met en zonder adrenaline voor gecombineerde femoralis/ischiadicus blokkade. Patiënten kregen 60 ml ropivacaïne 0.75% zonder (Groep R), dan wel met adrenaline 5 µg/ml (Groep RE) en veneuze bloedmonsters werden gedurende 48 uur na de blokkade afgenomen. Totale en vrije serum concentraties ropivacaïne bleven ruim onder de grens voor lokaal anesthetische systemische toxiciteit. De toevoeging van adrenaline verlengde de tijd tot de maximale concentratie significant, maar het verschil in de maximale concentratie was niet significant. Wat betreft duur van de pijnstilling, hebben we een groot, niet significant verschil gevonden in mediane tijd tot eerste postoperatieve pijnstilling (TTFR). Aangezien deze studie niet opgezet was om een verschil hierin te kunnen vinden, hebben we de studie

in hoofdstuk 5 opgezet om te onderzoeken of het toevoegen van adrenaline zorgt voor een significant langere TTFR.
In **hoofdstuk 5** hebben we dit verwachtte verschil in werkingsduur van postoperatieve analgesie niet kunnen aantonen. Achtendertig patiënten zijn geïncludeerd voor een echogeleid continu poplitea blok met ropivacaïne 0.75% zonder (ROPI) of met adrenaline 5 µg/ml (ROPI-EPI). We hebben de analgesie duur gemeten als tijd tot vraag naar eerste postoperatieve pijnstilling (TTFR) door de poplitea zenuwkatheter. Het niet vinden van een significant verschil zou kunnen worden verklaard doordat ropivacaïne zelf vaatvernauwende effecten heeft. Het kan echter ook komen door een type II fout vanwege een grote variatie in TTFR tussen de verschillende patiënten.

Postoperatief verlengde werking met een perifere zenuwkatheter
Als postoperatief langdurig pijn te verwachten is zoals bijvoorbeeld bij gewrichtsvervangende operaties, kan een zenuwkatheter achtergelaten worden voor langdurige infusie van lokaal anestheticum. Continue infusie kan gegeven worden door stimulatie en niet stimulatie katheters.
De studie in **hoofdstuk 6** is opgezet om te onderzoeken of er een correlatie bestaat tussen de minimale elektrische stroom (MEC) op de punt van een stimulatie katheter en de doeltreffendheid van een interscaleen katheter, uitgedrukt in 24 uur postoperatieve morfine consumptie. De afwezigheid van een correlatie tussen de MEC en de postoperatieve morfine consumptie zoals gevonden in hoofdstuk 6 indiceert dat de MEC geen voorspellende waarde heeft met betrekking tot de postoperatieve doeltreffendheid van de zenuwkatheter. Dit betekent dat de extra kosten van de stimulatiekatheter niet worden gecompenseerd door een betere werking.

Hoofdstuk 7 van dit proefschrift geeft een samenvatting van de resultaten, bediscussieert de belangrijkste bevindingen in relatie tot de huidige literatuur en geeft aanbevelingen voor toekomstig onderzoek.

Dankwoord

Dankwoord

Yes, big smile :D mijn ‘boekje’ is bijna klaar! Jaren geleden ben ik aan dit avontuur begonnen en daar gaat nu toch echt een eind aan komen (of het is een begin van mooie nieuwe dingen!). In deze tijd heb ik ontzettend veel geleerd en vele leuke, mooie (soms ook vervelende) en leerzame ervaringen op kunnen doen. Gevoelsmatig ben ik er een veelzijdiger clinicus van geworden, persoonlijk ben ik zeker gegroeid. En daar ben ik veel mensen zeer dankbaar voor, al dat werk doe je uiteraard niet alleen.

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Curriculum Vitae

Curriculum Vitae

Karin Petronella Wilhelmina Schoenmakers was born on October 13th, 1983 in Nijmegen, the Netherlands and spend her childhood in Sint Anthonis (NB). After finishing high school SG Stevensbeek (major Nature and Health with French) in 2002, she moved to Nijmegen to study medicine at the Radboud University.
During medical school she became interested in pain medicine and she did an anesthesiology and pain medicine internship. Her scientific internship was about DNIC and prediction of acute pain after total knee- and hip arthroplasty, supervised by Dr. O.H.G. Wilder-Smith.
She received her medical degree in 2009 after which she started working as an anesthesiology research fellow at Sint Maartenskliniek on different aspects of peripheral nerve blocks under the supervision of Dr. R. Stienstra. This was the foundation for this thesis.
In 2012 she started her anesthesiology residency at Radboud University Medical Center under prof. G.J. Scheffer during which this thesis was finalized. Her interest for Regional Anesthesia and Pain medicine continues, as she is now the resident representative board member of the European Society of Regional Anaesthesia and Pain Therapy while finishing her residency.

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